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8. hemochromatosis 9: tumors
10 hepatic abscess 11. amyloidosis
12. parasitic diseases
13. gallbladder diseases
14. bile ducts diseases

DISEASES of the LIVER

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With a Foreword by
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Philadelphia and Montreal

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Second Impression

Distributed in Great Britain by
Pitman Medical Publishing Co., Limited, London

Library of Congress Catalog Card No. 55-9161

Printed in the United States of America

4283

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N56

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Diseases of the

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Dedicated to all those who tread the paths
leading to the better understanding,
prevention and cure of liver disease

FOREWORD

CECIL J. WATSON, M.D.

In the history of biology and medicine the liver has emerged but slowly and ponderously from its sea of mystery. Bartholin's relegation to the simple role of a "large dull bile producer" steadily gives way, in the light of modern study, to the Galenical speculation that the liver is "maximus heroibus." As day by day, in this era of enzyme chemistry, the story of the liver's countless transmutations and syntheses unfolds, one is impressed that here is a philosopher's stone undreamed of by the natural philosophers of ancient and medieval times. Their knowledge, indeed even their speculation, was so limited that with "all science as their province" a special treatise on the liver could hardly have been anticipated. Yet so many of these early students gave attention to the liver in considerable degree that its medical history includes a reasonably complete roster of the outstanding medical scientists at least until the middle of the nineteenth century.

No doubt because of the fascinating array of differing clinical manifestations, the purely clinical study of liver disease appears to have stimulated the first really significant, individual treatises on the liver. The books of Budd and Saunders, of a century ago, were remarkable for their time and contain observations of great value, even to the present day, although they now receive too little attention. Thus for example, Budd clearly recognized bilirubinuria without jaundice and described cases that probably represented hepatitis without jaundice, although no general recognition of this was to occur for more than 75 years. Saunders, stimulated by the problem of human obstructive jaundice, carried out some very penetrating experiments on the "reabsorption" or regurgitation of bile under the influence of slight increases of intrabiliary pressure. It is true that these only confirmed and extended, although much more precisely, certain earlier observations by Haller, "father of physiology." From Budd and Saunders, later Frerichs, Rolleston and McNee, Eppinger and to the present (Lichtman, Himsworth, Spellberg, Sherlock), it has been customary for a single author to range over the entire subject of the liver and its diseases on the basis of his own experience and study. This has the obvious potential advantage of greater unity and cohesion, with less opportunity for repetition. The volumes just referred to have made and are still making an important contribution. Yet, with the liver now revealed as embracing so much of science, medical and otherwise, the task for one author appears to be almost insuperable, if the work is to be reasonably comprehensive and at the same time deal accurately with special areas of experience and knowledge. The only alternative is the method used in the present volume—that in which an editor, widely instructed in the general topic himself, selects a group of colleagues, each especially suited by interest and experience, to deal with individual sections. This is not to champion ultraspecialization but simply to recognize that an individual with interest and activity in some broad field should devote himself more intensively to the study of certain specific problems within that field. During the past decade there have been several groups of investigators in the United States which have met at regular intervals to discuss problems of liver disease, including such widely divergent ones as the virology and the epidemiology of hepatitis, serum protein alterations in liver disease, disturbances of steroid metabolism due to liver injury, pigment metabolism in hepatic cirrhosis, the etiology and the pathology of human cirrhosis, experimental dietary cirrhosis, and many others. It is safe to say that the exchange of information and the stimulus of ideas between virologists and metabolists, or physiologists and clinicians, has been of no little value in pushing forward information about the liver along a broad front. The fruit of such meetings is bound to be represented in the chapters of this book, since they have been written, in the main, by participants.

There is no doubt that the method of collaboration invites overlapping and presentation of various or even divergent points of view. It is perhaps less likely to favor dogma or the ultra-authoritarian attitude. It would be surprising, at least in the present state of our knowledge of liver disease, if one could not find points for disagreement in the chapters of this book, which to some extent must represent individual opinion and concept. At the same time it is believed that for the most part, controversial issues are presented fairly, so that the reader can at least recognize the basis of disagreement; from there on, of course, he is "on his own."

As research begets research, and as there is throughout the world a veritable crescendo of increased participation in research, it is not surprising that science is steadily less static and that all scientific books are likely to become obsolete in a much shorter period than was true even two or three decades ago. Herein lies another advantage of the collaborative method, as early and frequent revision is much more readily feasible than in the case of a book written entirely by a single author.

It appears to the writer that Dr. Schiff and his collaborators have brought together in this book the more important information presently available about diseases of the liver and closely associated topics. They are to be congratulated on achieving this with good judgment and clarity.

PREFACE

In the recent words of Himsworth, the present time seems to be particularly opportune for reviewing our knowledge of liver disease. A partial list of reasons would include the advances made in the fundamental sciences as they pertain to liver structure and function; the advances in the experimental approach to liver disease; the increased knowledge in the field of viral hepatitis; the newer clinical criteria and concept of hepatic coma, with attention focused on disturbance in the metabolism of ammonia; a better understanding of the pathogenesis and the treatment of cirrhosis; a clearer concept of the metabolic defect in hemochromatosis and the apparent effectiveness of depleting iron stores in the treatment of this disorder; the implication of disturbed copper metabolism in hepato-lenticular degeneration; the increasing experience with needle biopsy of the liver; and the surgical attack on portal hypertension.

This book is not intended to be encyclopedic in nature but rather the expression of present-day information pertaining to various aspects of liver disease by a group of authors particularly qualified by their experience, interest and scientific contributions. The reader may discover certain omissions; but he usually will find these to be matters of lesser importance. They will be more than compensated by the quality of the information contained, which deals with those aspects of hepatic disease that are much more apt to concern him, including the description of the principles of treatment, both medical and surgical, by experts in the field. Furthermore, he will frequently find it unnecessary to consult other books, particularly on points dealing with basic concepts.

To the various contributors the editor expresses his deep gratitude for their excellent and willing co-operation. He has considered it good fortune indeed to have been associated with them in this undertaking. He wishes to express his thanks to Cecil J. Watson, Arthur J. Patek, Jr., and to his colleague, Edward A. Gall, for their helpful suggestions. He is particularly indebted to Miss Olive Mills, without whose tireless and able secretarial and editorial assistance he would not have been able to accomplish his task.

In some instances individual authors have appended acknowledgments of assistance to their respective chapters. To those concerned the editor wishes to express his apologies for not having included these expressions of gratitude for the sake of uniformity of composition and conservation of space.

LEON SCHIFF

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Chapter 1

ANATOMIC CONSIDERATIONS

Aron M. Rappaport, M.D.

The time when anatomy consisted of tabulated data from the dissecting rooms has passed. These data from the "House of the Dead" came to life when each dissected compartment of our body was used to illustrate its activities that contribute to the maintenance of the organism as a whole. Today, the work of anatomists and physiologists interlaces continuously. Indeed, the concepts of the morphology of the liver have changed with the advances in hepatic physiology and pathology. Experimentalists and clinicians too have added to the knowledge of normal and abnormal morphology. Functional anatomy is thus on the march, and we shall strive to follow it in our presentation.

In the following pages the development of the liver, its lobes, surface, peritoneal connections (ligaments), its micro-anatomy, vessels and nerves will be considered. Also, the bile ducts and the gallbladder and the general topography will be discussed.

The liver is covered by the fibrous capsule of Glisson, which, in turn, is invested with serosa. At the porta hepatis this capsule turns deep into the liver substance along the vessels and the biliary ducts, following them to their finest ramifications.

The liver of an adult weighs from 1,400 to 1,600 Gm. In the adult it comprises one fiftieth of the body weight. In the newborn, the greater comparative size of the liver, (one twentieth of the body weight), is due to its blood-forming activity during fetal life. Although it is the largest gland of the body, it is believed to yield a relatively small amount of secretion (600 to 800 cc. of bile). The hardened adult specimen in situ has the appearance of a wedge with the base to the right. The normal liver extends from the right fifth intercostal space in the midclavicular line down to the right costal margin. The lower margin of a normal liver usually transgresses the costal border. The greatest longitudinal diameter of the liver is near its right lateral surface, where it measures from 15 to 17 cm.; its greatest thickness (12 to 15 cm.) is at the level of the upper pole of the right kidney, and its greatest transverse diameter is from 15 to 20 cm. A convenient site of transthoracic puncture for liver biopsy is in the anterior axillary line at the seventh, the eighth or the ninth interspace, always one interspace below the upper limit of liver dullness. The morphologic and the topographic variations of the normal liver were studied recently by Villemin and associates.[169]

EMBRYOLOGY

The liver arises from the entodermal lining of the foregut during the fourth week. The hepatic diverticulum is situated at the ventral side of the foregut, cranially to its opening into the yolk sac. In embryos of 5 to 6 mm. length, the original hepatic diverticulum can be distinguished as differentiating cranially into proliferating hepatic cords and bile ducts, caudally into the gallbladder. The hepatic tubular cords sprout tridimensionally (cranially, ventrally and laterally), penetrating the septum transversum and passing between the 2 layers of splanchnic mesoderm. The latter envelop the sprouting lobules, provide their interstitial connective tissue and form the liver capsule. Strands of entodermal epithelium growing into the septum transversum enclose islets of proliferating mesenchymal cells which later will sacculate and be transformed into sinusoids. These groups of cells remain always in contact with the rest of the mesenchyma surrounding the liver anlage. In the human liver the latter is never in the state of a compact mass.[106] In a human embryo of 26 somites, irregular masses can be observed developing in a frontal plane. Their strandlike form might be due perhaps to the early vascularization of the human septum transversum, between the vessels of which the hepatic cords penetrate. These enlarge at their bases later, fuse and arrange themselves into lamellae and plates. Thus the human liver, initially a simple gland, changes into a "composite labyrinthine gland."[19] Although the differentiation of the liver anlage is conditioned by the interrelation of both entodermal and mesenchymal elements, still the primary factor remains the proliferation of the epithelium in tubular cords that communicate with the bile ductules.

The prevailing growth, to right or to left, will determine the shape of the liver and the relative size of the lobes. Budding parenchyma, by losing continuity with the liver anlage, may give rise to accessory liver masses. A primary dystopic liver anlage might be the cause of an associated right diaphragmatic hernia.[10]

The primordium of the gallbladder is a diverticular dilation of the original outgrowth from the gut, situated caudally to the confluence of the hepatic ducts. As it elongates quickly and becomes saccular, developmental disturbance in this region can produce malformations of the gallbladder in the presence of a normal liver. Aberrant biliary ducts, *vasa aberrantia,* are considered by most authors to be proliferating branches of primitive tubular liver cords that were arrested in their development. They occur in the left triangular ligament on the inferior surface of the diaphragm, in the spigelian lobe, around the gallbladder, in the furrow of the umbilical vein and at the level of the attachment of the suspensory ligament, and are of surgical significance.[146]

Anomalies in the blood supply of the liver are due to anomalies of the vascular anlage rather than of the liver anlage.

Summary: The liver is an entodermal outgrowth of the foregut into mesodermal surroundings in order to increase the metabolic and digestive activities of the gut. The growth of the liver is accomplished by tridimensional budding of the bile ductules, which continue to be the centers of the small parenchymal masses which they form. The final shape of the liver and its attached excretory apparatus is an expression of the developmental case history of the organ.

LOBES

As distinguished from the multilobulated liver of many mammals, the human liver is one compact and continuous mass. However, it is divided conventionally by the line of insertion of the falciform ligament into 2 lobes. The right lobe is larger and shows on its posterior-inferior surface two smaller lobes, the caudate and the quadrate lobes. The former with its caudate process is wedged between the groove of the inferior vena cava and the porta hepatis. The quadrate lobe lies between the round ligament and the gallbladder. Cantlie[24] and Sérégé[157, 158] considered the gallbladder-caval line as the true dividing line of the liver. Hjortsjö[77, 78] injected the hepatic ducts in situ with red lead in celloidin and took stereoscopic cholangiograms. Then he filled the portal vessels with colored celloidin, corroded them and described their course in relation to the stereogram. In his corrosion specimen he saw a fissure running toward the caval area from the right septal fissure, which is situated to the right of the gallbladder fundus. Occasionally, there were other fissures subdividing the left lobe. In fact, these fissures harbor major branches of the hepatic vein and are bridged in vivo by sinusoids.[48]

With a view to operations upon the parenchyma, Couinaud[31a] and Junès[85a] have recently extended the study of the distribution of the vascular and biliary tree within the liver and found it to be strictly segmental. While Couinaud likens the different segments in the liver to the lobes of the lung, insisting upon segmental resections of the liver, Junès objects to this view because the portal and the hepatic venous systems of the liver segments do not coincide in their distribution and orientation. Besides, the segments of the liver are not separated by a serous membrane similar to the visceral pleura enveloping the pulmonary lobes. Thus we must say that the liver is *one* parenchymal mass and that the lobes are not delimited by any

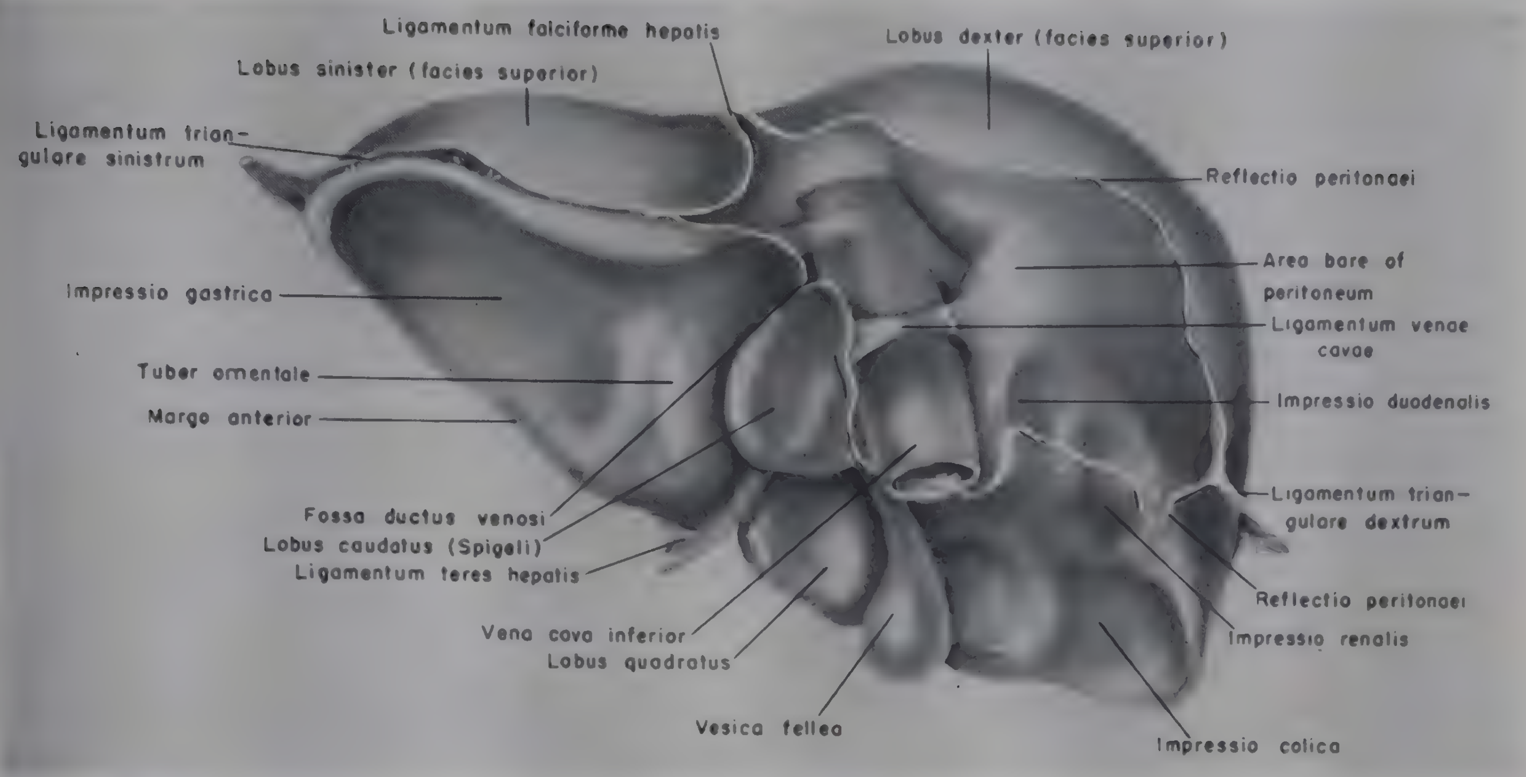

Ligamentum falciforme hepatis
Lobus dexter (facies superior)
Lobus sinister (facies superior)
Ligamentum triangulare sinistrum
Reflectio peritonaei
Impressio gastrica
Area bare of peritoneum
Ligamentum venae cavae
Tuber omentale
Impressio duodenalis
Margo anterior
Ligamentum triangulare dextrum
Fossa ductus venosi
Lobus caudatus (Spigeli)
Ligamentum teres hepatis
Reflectio peritonaei
Impressio renalis
Vena cava inferior
Lobus quadratus
Vesica fellea
Impressio colica

FIG. 1. Posterior view of the liver. The marks impressed by neighboring organs upon the liver surface mirror its intricate topographic relation with the surroundings. (Anson, B. J., Maddock, W. G.: Callander's Surgical Anatomy, ed. 3, Philadelphia, Saunders)

fibrous septa traversing the liver substance. Each of the conventional hepatic lobes has its own vascular and biliary systems, but there are intercommunications between the respective systems. Surgical anastomosis of a major intrahepatic bile duct of one lobe with an intestinal loop will drain the entire liver.[109, 107] Although preferential blood flow to the right or the left liver lobe has been proved by injection of radioactive phosphorus into the mesenteric vein,[65] there is sufficient mixture in the streamlined flow and intercommunication between the vascular channels to guarantee unity of function of the organ.[155, 114] Also, splenic portography shadows the entire liver at once.[43] Furthermore, of all the liver functions none ever has been attributed to any one lobe. From a developmental and microstructural viewpoint, however, the liver is to be considered as lobulated not only on its surface but also into its innermost parts (p. 10). The accessory lobes scattered in various organs (mesentery, suspensory ligaments, spleen, adrenals) are the remainders of parenchymal clusters around the sprouting bile ducts that have split off from the entire liver mass. Some abnormal lobulation may have been due to pathologic processes during intrauterine life. Riedel's lobe is a downward prolongation of the right liver lobe often caused by an adhesion to the mesocolon.

Summary: The liver consists of a uniform mass of parenchyma which conventionally appears to be divided into lobes by deep vascular or avascular grooves. In spite of the bilateral portal blood flow, there is not enough evidence to prove that the named lobes of the adult liver have distinct functions. On the microscopic level, however, the liver is lobulated throughout.

SURFACE OF THE LIVER

Of the 5 surfaces of the liver (superior, anterior, right lateral, posterior and inferior), the posterior and the inferior show more structural features.

The *superior,* the *anterior* and the *lateral* surfaces are smooth and shaped convexly to fit into the dome of the diaphragm. They are completely covered by peritoneum except for a small triangular area where the 2 layers of the upper part of the falciform ligament diverge.

In the marks of the *posterior* and the *inferior* surfaces of the liver (Fig. 1) we can read a glorious past, when the liver represented one fifth of the entire body weight. The groove of the venous ligament separating conventionally the left liver lobe from the rest of the organ is the site where the gastrohepatic omentum is inserted. Once in this furrow lay a main afferent channel that brought oxygenated blood from the umbilical vein into the hepatic sinusoids. Some of the blood in this channel also passed through the venus duct (duct of Arantius) directly into the inferior vena cava and so to the right atrium. The umbilical vein, an arterial channel now obliterated and transformed into the round hepatic ligament, runs in the lower half of its groove. It delimits the quadrate lobe from the left liver lobe. Thus from the beginning the liver, and especially its left lobe, has had arterial blood of first quality.

A third vascular channel, the inferior vena cava, runs through the posterior surface of the liver at the base of its bare area. In some livers the vein passes under a bridge of liver substance. Here the hepatic veins, arranged in a superior group of 3 (left, right and median hepatic) with a variable inferior group, empty into the inferior vena cava. Thus the coronary ligament attaching the triangular bare area of the right liver lobe to the diaphragm by areolar tissue encloses the above large veins.

The fossa of the gallbladder delimits the quadrate from the right liver lobe. The horizontal portal fissure, which joins the upper ends of the gallbladder fossa and the groove of the round ligament, contains afferent and efferent structures. These are the branches of the hepatic artery and the portal vein and the hepatic nerve plexus entering the liver, and the hepatic ducts and the lymph vessels emerging. In the portal fissure the arterial branches lie between the bile ducts in front and the portal branches behind. Had it not been for the caudate process of the same lobe, the noble organ, Hepar, would have had its initial "H" perfectly grooved on its posterior and inferior surface. Grooves are not always the remains of developmental events. They result also from the folding of the liver mass in a limited space.[19]

The diaphragmatic, renal, suprarenal, colic, duodenal, pyloric, gastric and esophageal areas that we see on a posterior view of the liver are the impressions made by neighboring organs. These imprints should remind us also of a variety of pathologic processes that can involve the liver together with any one of these organs.

Generally speaking, the surface mirrors what is close to it and is exposed to injury from its surroundings.

PERITONEAL CONNECTIONS: LIGAMENTS

The liver is connected to diaphragm, abdominal wall, stomach and duodenum by bands of connective tissue in peritoneal folds. These have the role not only of helping to maintain the organ in position but also, at least as important, the function of conveying afferent, efferent and collateral blood vessels, lymphatics and nerve plexuses to the liver.

Falciform Ligament. This peritoneal fold connects the liver to the diaphragm and the anterior abdominal wall. It ascends from the umbilicus, from which during fetal life it conducted the umbilical vein to the liver. The obliterated vessel forms the free edge of the sickle-shaped peritoneal fold. It carries between its peritoneal layers the para-umbilical veins, the clinically important collaterals of the portal vein. When dilated in cirrhosis they permit blood samples to be drawn from the portal area which then can be made visible by injection of radiopaque material through the same veins.[161]

Coronary Ligament. The "bare area" of the posterior surface of the liver, connected by areolar tissue with the diaphragm, is enclosed by an upper and a lower layer of peritoneum. The inferior vena cava and the hepatic veins are contained within the coronary ligament.

Hepatorenal Ligament. The lower layer of the coronary ligament, passing along the lower limit of the right posterior hepatic surface, may be reflected on the upper part of the anterior surface of the right kidney, thus forming the hepatorenal ligament. It often contains collateral vessels of the liver.

Right Triangular Ligament. This is the free margin of the coronary ligament.

Left Triangular Ligament. This consists of 2 closely applied layers of peritoneum that continue with the falciform ligament in front and the lesser omentum behind. Both triangular ligaments, besides attaching the liver lobes to the diaphragm, convey collateral branches from the phrenic and the musculophrenic vessels to the liver.

Ligaments are ties that connect the organ with the rest of the organism. Through them nutrients, hormones, raw materials for function, and stimuli are carried in and out by blood and lymph vessels, by ducts, and by nerves.

MICRO-ANATOMY

HEPATIC CYTOLOGY

In describing the minute structure of the liver, a brief discussion of hepatic cytology is essential. It provides the basis for hepatic histochemistry, the study of the chemical changes within the hepatic parenchymal cells, which has become a routine procedure in the investigation of the physiology and the pathology of the liver. Recalling Soskin's[163] statement that the quantity of tabulated enzymes contained in a muscle cell leaves little or no room for the presence of any purely structural protein, one may expect at least a similar balance in the cytoplasm of the metabolizing liver cells. Indeed, because of their rich content in enzymes the major part of all cytoplasmic and cytochemical studies is done on hepatic cells. The literature on the microscopic and the electron microscopic studies of hepatic protoplasm is growing; the nomenclature is in flux. Histologists, biologists and biochemists join in their efforts to investigate the function of the protoplasmic organelles, the aspect of which reminds one of the infinite marvels of the deep-sea flora. However, the enthusiast for the great achievements of the electron microscope should bear in mind that the world is infinite not only upward but also downward. Considering the hepatic cell as a part of this infinity and looking at it through the optical instruments at present available, the following can be described.

The hepatic parenchymal cell isolated from a fresh piece of liver is more or less rounded. After fixation, it takes a polyhedral form, presenting 6 to 8 surfaces. These surfaces are enmeshed by a ring of bile capillaries, excepting the one contiguous with the sinusoids. The diameter of the cell varies between 18 and 26 μ. It contains one or two, rarely several, nuclei that are well developed. Because of intensive metabolic activity the hepatic cell is rich in mitochondria, ergastoplasm and inclusions. It possesses a "Golgi apparatus," which, however, as in cells of other organs, is much debated.

Nucleus. The hepatic nucleus shows its open face even to the freshman in histologic studies. This appearance is due to its width (up to 12 μ in the human, up to 24 μ in the mouse), to the amount of nucleoplasm within the distensible nuclear membrane and to the fine network of chromatin granules or flakes. The greater amount of intranuclear chromatin substance present is evidence of the phenomenon of polyploidy, the study of which is favored in the hepatic cell. The chromatin particles contain DNA (desoxyribonucleic acid) and show a strongly positive Feulgen reaction. They lack RNA (ribonucleic acid) and have only small amounts of acid and alkaline phosphatase.[175] Multiplication of the number of chromosomes is obtained also by the presence of 2 and more nuclei in some hepatic cells. Multinucleated cells are found frequently in the regenerating liver, which is, therefore, the preferred organ of study for the problem of regeneration. A method for isolating nuclei of rat liver cells was described by Dounce.[42] The hepatic nucleus has from 1 to 2 distinct nucleoli. Frequently, inclusions are observed in the nucleus, e.g., fat droplets, pigments, granules and rarely crystals.

Cytoplasm. The structural details of the cytoplasm will be discussed under the headings of mitochondria, ergastoplasm, Golgi apparatus and cellular inclusions.

MITOCHONDRIA. The liver cell is very rich in mitochondria. About 2,500 mitochondria are present in a rat's liver cell, and their number can be used as a unit of measurement of regeneration.[3] These small cytoplasmic organs perform a multitude of enzymatic reactions. When looked at in ultraviolet light they glow in their activity with blue autofluorescence.[68] Mitochondria can be isolated by differential centrifugation[27] and obtained in a pure form by using a sucrose solution.[79] They contain 65 per cent protein,

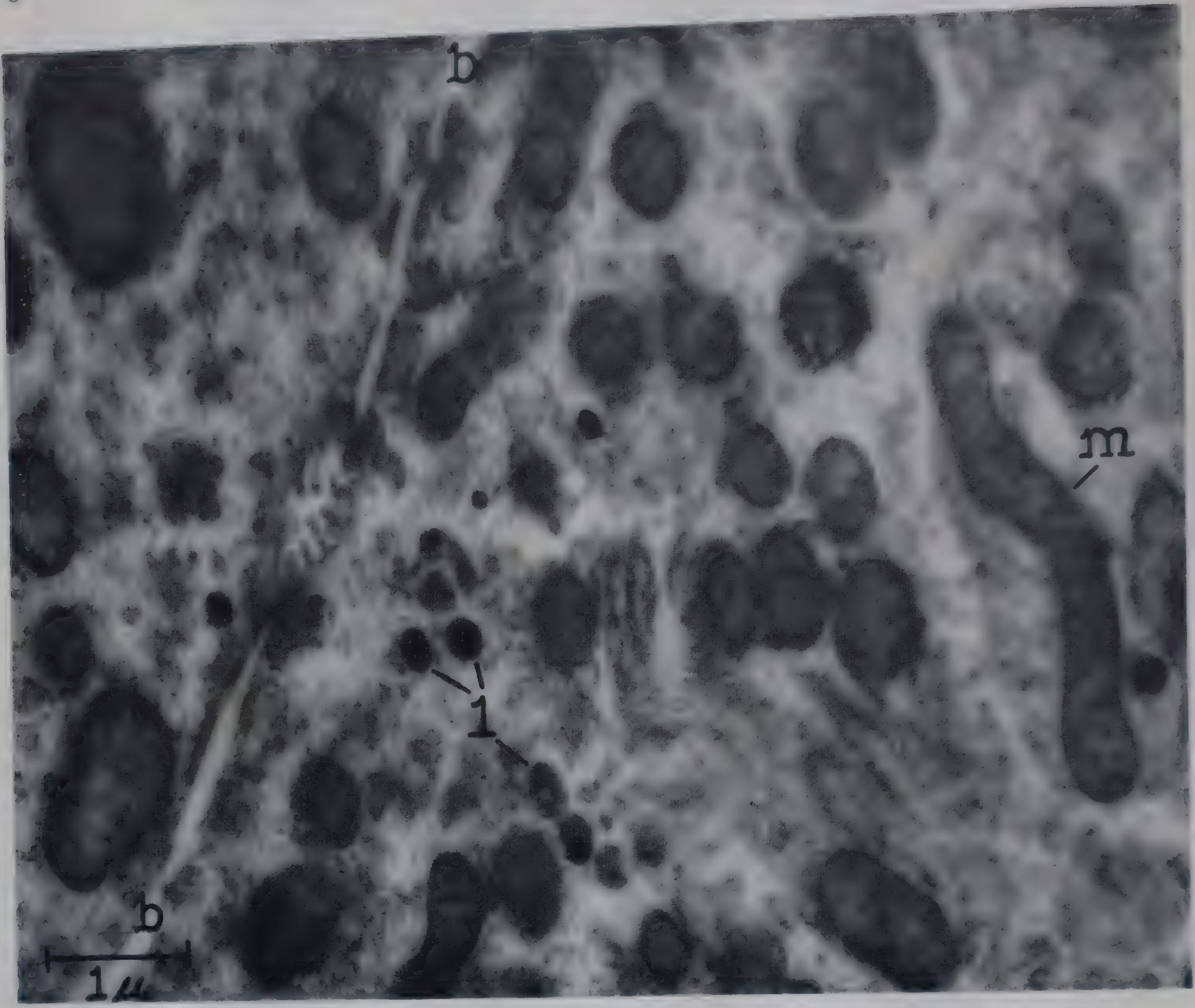


FIG. 2 A. Part of two adjacent parenchymatous cells from a rat liver. "The boundary between them runs from *b* to *b*; note along it the cross section of a bile capillary with a number of fine *papillae* protruding into its lumen. Numerous mitochondria cut at various angles appear in the picture as sharply outlined areas more dense than the rest of the cytoplasm. Most mitochondrial profiles are circular or oval, but at *m* an elongated profile measuring 3.5 μ in length can be seen. Note the wide variation in mitochondrial diameters. Most of the mitochondria in this figure show a limiting membrane and a certain amount of internal structure, which does not appear clearly because the section is too thick. Several lipoid inclusions (1) can be seen in the figure mostly in the vicinity of the bile capillary. × 18,000 × 13,500." (Palade, G. E.: Anat. Rec. 114:427)

35 per cent lipid material[9] and some RNA. Recent studies of the mitochondria with the electron microscope have demonstrated their inner shelved structure (Fig. 2, A and B) and have shown that they are bounded by a membrane that separates them from the rest of the cytoplasm.[136] This "barrier of availability"[101] may illustrate how deeply the principle of limitation is imprinted even upon the microconstituents of our cells. The diameter of the mitochondria varies between 0.35 and 0.74 μ and their cristae are thin and irregularly spaced.[136] These internal ridges of the cytoplasmic organelles appear as the most probable location for the postulated enzymic chains. The close arrangement in the hepatic mitochondria of about 16 active enzymes and vitamins instrumental in the tricarboxylic acid cycle and in other oxidative and synthetic processes represents the morphologic aspect of the stepwise oxidation and reduction of a substrate essential in these biochemical reactions.[96, 87, 88] All these structural details seen in the range of

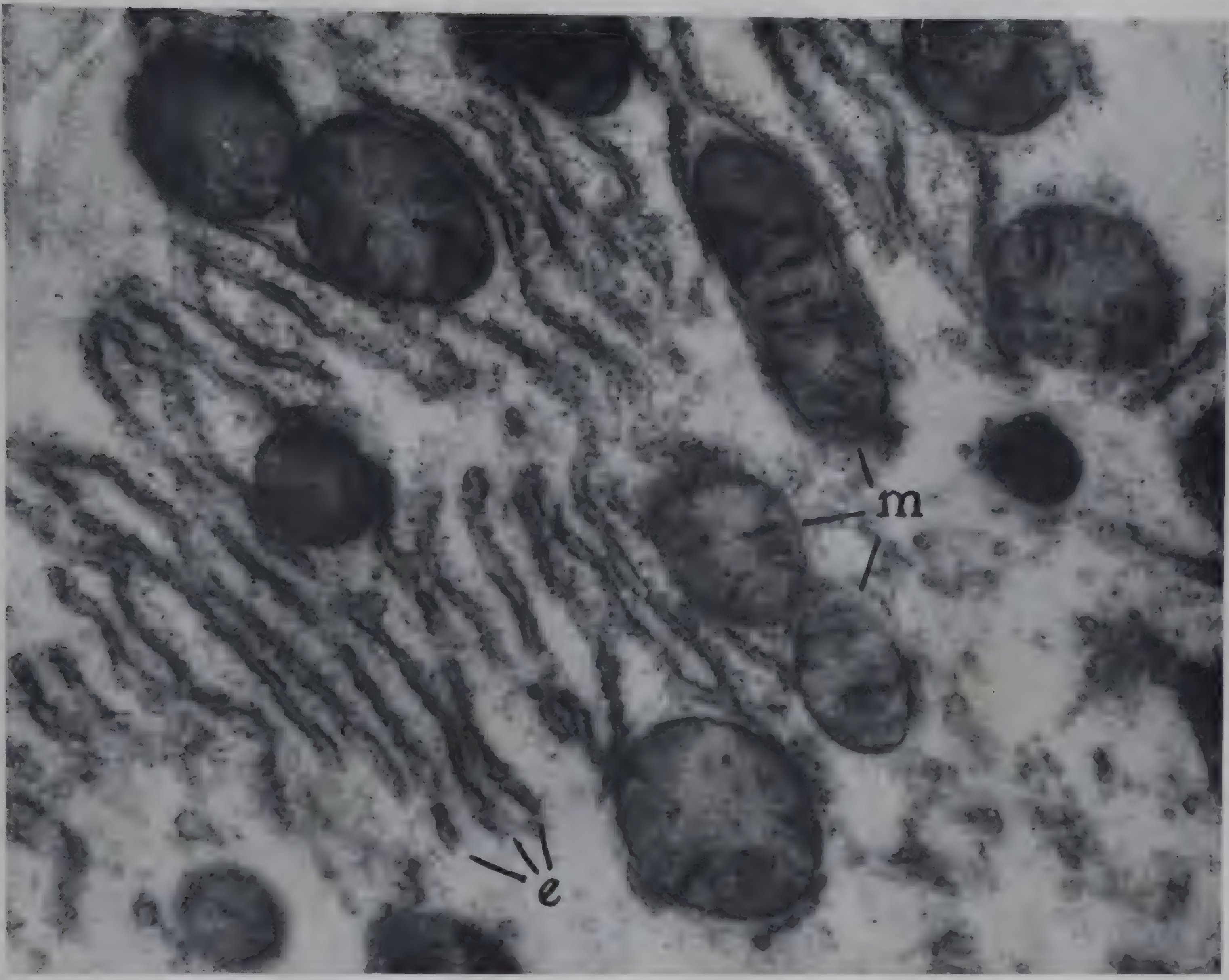


FIG. 2 B. Higher magnification of a small field in the cytoplasm of a parenchymatous liver cell (rat). There are longitudinal, oblique and transverse sections of mitochondria (m) in this field. Their membrane varies in density and thickness and is doubled in some places. Dense bands project like shelves from the membrane into the matrix of the mitochondria which is denser than the matrix of the ground substance of the cytoplasm. Note the presence of a large number of tubular structures in this ground substance. They form an endoplasmic reticulum (e) among the mitochondrial profiles. × 71250. (Palade, G. E.: J. Histochem. & Cytochem. 1:188)

the electron microscope suggest a very complex organization at the molecular level (Fig. 2 B).

ERGASTOPLASM. Another feature of the hepatic cytoplasm is its basophilic material, now called ergastoplasm, a term that has organelle implications.[67] In cells that manufacture protein these cytoplasmic organelles are very prominent. As this is the case with the liver cells, their ergastoplasm can be demonstrated easily by electron microscopy. This cytoplasmic material is rich in RNA protein and is described as an endoplasmic reticulum that is made up of canalicular and vesicular elements[137] (Fig. 2 B). Recently, J. M. Weiss,[171] studying these canalicular elements in the cell of the pancreas, came to the conclusion that they are collapsed sacs; he called them ergastoplasmic sacs. When the cells are homogenized and broken down for differential centrifugation, the ergastoplasm yields submicroscopic matter, the microsomes.[28] These microsomes are considered to be endowed with the property of "self-duplication."[28] They are free of enzymes (except for thromboplastin) and contain about 50 per cent of the RNA of the cell. However, not all microsomes derive from organized ergastoplastic structures. Palade[135] observed a granular component of

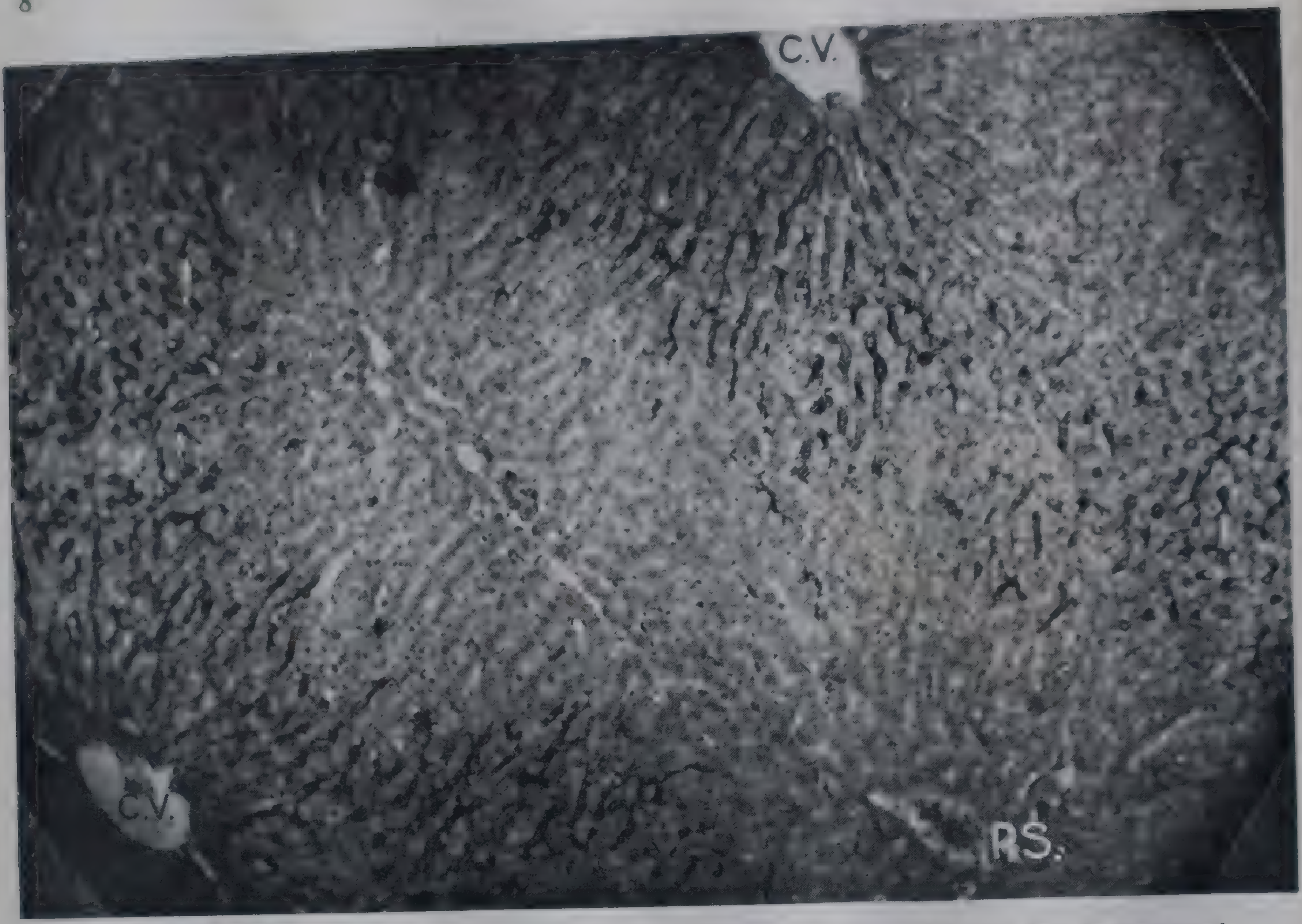


Fig. 3. Acinar unit in the liver of a rabbit. The area clear of India ink is centered around the axial channels that grow out from a small portal space (P.S.). It extends into 2 adjacent hexagonal fields, the central veins of which (C.V.) are seen in the left lower and right upper corner (× 100 approx.). (Rappaport, A. M., Borowy, Z. J., Lougheed, W. M., and Lotto, W. N.: Anat. Rec. **119**:11)

the ergastoplasm in situ. Hepatic tumor cells are characterized by a relative lack of canaliculi (flattened sacs) but have a substantial content of granules; hence the latter seem to be related to growth.[80] As the content of the RNA in the cytoplasm is an indication of protein synthesis in the cell, this metabolic activity can be studied quantitatively after fasting and after refeeding. In starvation the cells close to the terminal portal branches lose their basophilic substance first; after refeeding they replenish their losses last. Cells close to the central veins behave inversely.[97] Similarly, the genesis of ergastoplasmic sacs rich in RNA was observed by J. M. Weiss[171] in the cells of the pancreas of starved and of refed Swiss albino mice. There is a large increase in ergastoplasmic sacs in the refed mouse. One marvels at this primitive behavior on the part of skillful cells, members of specialized cell complexes. When carrying out metabolic function they behave as though they were individuals with an avidity for greater surface as unicellular organisms in digestive function.

Golgi Apparatus. The "Golgi apparatus" in the liver cell is as much debated as that in other organs. Its demonstration in mammals is more difficult than in amphibians. The presence of glycogen in the parenchymal cells alters the diffusion of reducing substance in the cell. Ludford[110] impregnated a "Golgi apparatus" in glycogen-depleted cells of rodents. It formed a network between nucleus and bile canaliculus during bile secretion and stored vital dyes near the apparatus. Recent studies with the electron microscope still have not settled the controversy about the "Golgi apparatus." While Dalton[32, 33] claims its existence, others deny it. It seems that, in spite of her silvery curls, the "elusive woman"[67] will continue to attract many curious men.

Cytoplasmic Inclusions 1. *Glycogen.*

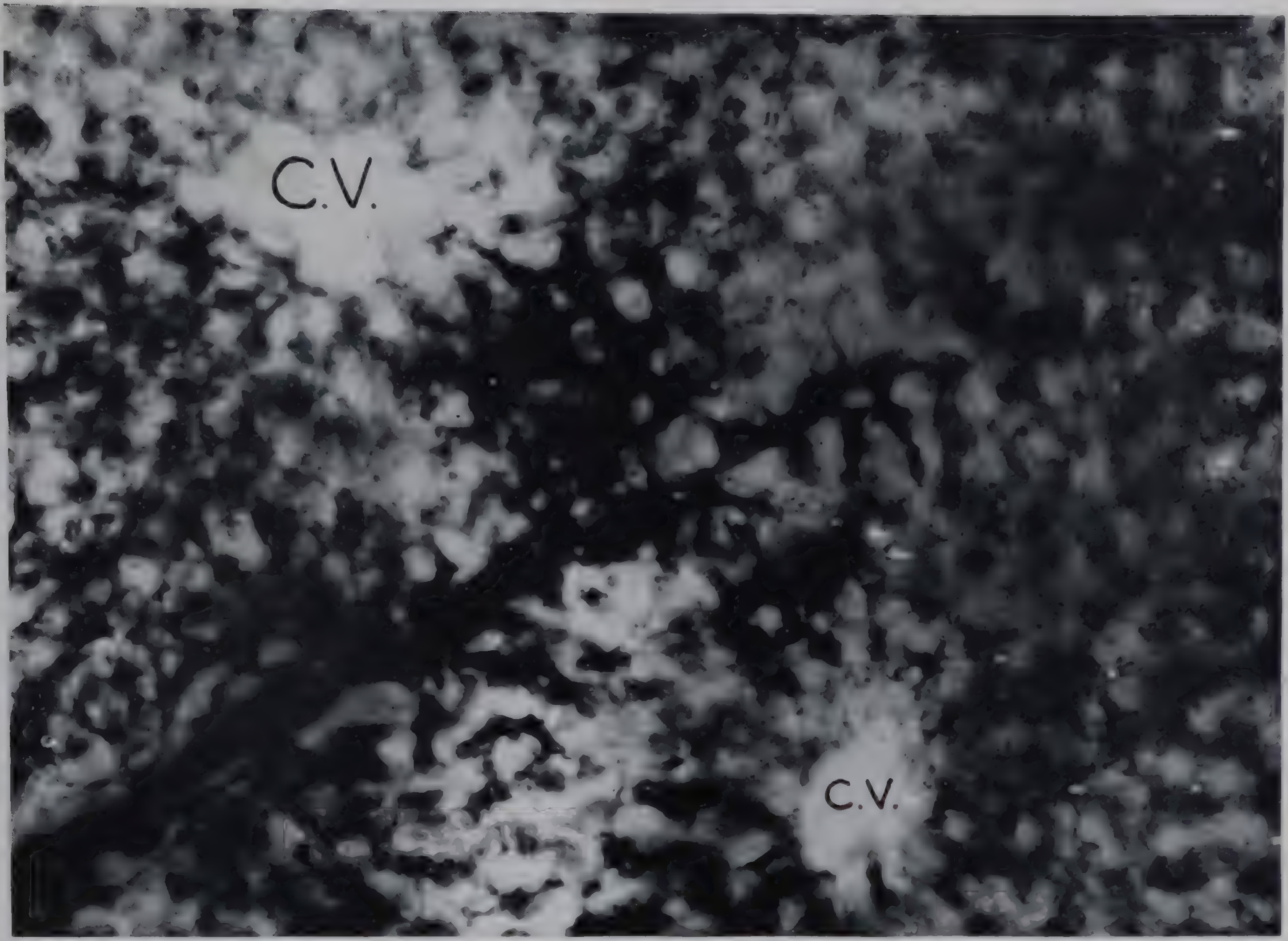


FIG. 4 A. Liver acinus in a human liver. The acinus occupies sectors only of 2 adjacent hexagonal fields and reaches their central veins (C.V.). The axial terminal portal branch of the structural unit is injected with India ink and runs perpendicularly to the two hepatic (central) veins with which it interdigitates. It is visualized by a fortunate cut parallel with almost its entire length. The central veins lie close to each other in this section. (Thick cleared section × 300)

The inclusions of the hepatic cell vary with its metabolic state. The glycogen-filled cells of a rabbit that has indulged in carrots before sacrifice, and the biopsy from a dog's liver afford good examples of glycogen inclusions. The tissue has a honeycomb appearance. Glycogen is stored first but released last around the central vein.

2. *Fat inclusions* have followed the opposite distribution within the hepatic parenchyma. The "depot-fat" brought into the liver during starvation[9a] shows up first in the cells of the area close to the afferent vessels. Intracellular accumulation of lipids due to dietary choline deficiency will become manifest first around the central veins. Larger fat globules can produce a signet-ring appearance in the cell. Accumulation of fat globules may finally disrupt the cell membrane and form fatty cysts extracellularly.[69, 71]

3. *Protein inclusions* can be demonstrated easily by histochemical methods. During starvation the pericentral cells maintain their protein inclusions much longer than the periportal cells. Bile pigments, iron and ceroid material are observed occasionally within the hepatic cytoplasm as a result of earlier or present pathologic changes.

HEPATIC HISTOLOGY

Even in its early stage of development the liver shows the close association of entodermal and mesodermal elements that characterizes this organ. The rows of epithelial cells radiating from the terminal portal vessels to the terminal hepatic (central) veins are sustained by fine reticulin fibers and sinusoidal capillaries of mesodermal origin. However, the amount of fibrous tissue around the afferent and the efferent channels is in

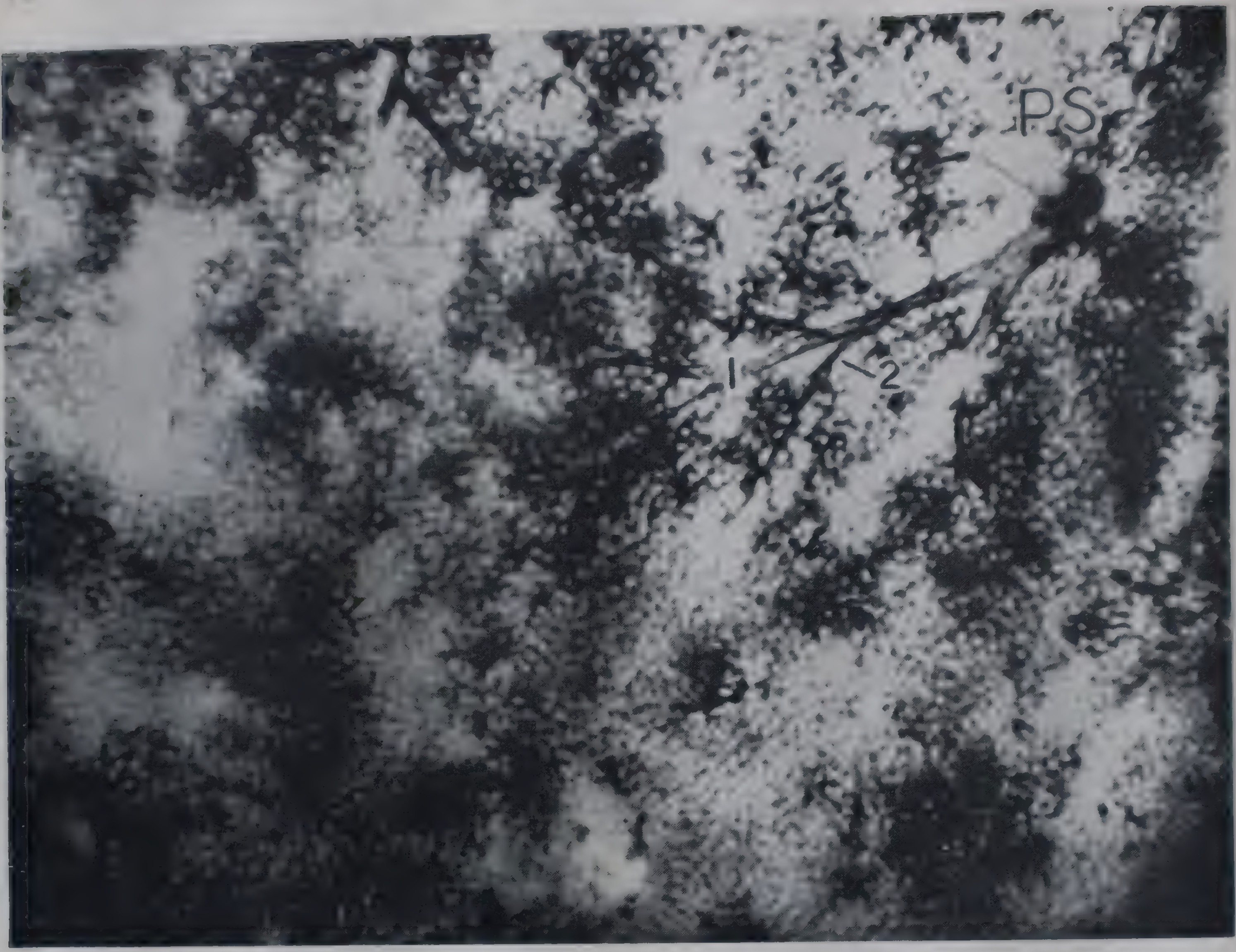


FIG. 4 B. Acinar agglomerate. Human liver injected with India ink. Three large portal branches grow out in different directions from a portal space (P.S. in right upper corner). One of these runs diagonally through the field and represents the axis of an acinar agglomerate. From this portal branch preterminal (1) and terminal (2) branches grow out and form the axes of the outcropping complex and simple acini respectively. (Thick 100 μ cleared section × 18)

proportion to their size. They are the continuation of Glisson's capsule, a remainder of the septum transversum. We may well think of the liver as a tree that has grown out from the virgin land of the foregut to increase its metabolic and digestive function. It has spread its crown of parenchyma into the space of the septum transversum but continues to draw its nutrients through the portal capillary roots from the rich soil of the intestine. As the liver anlage develops by tridimensional budding of the bile ducts to the final shape of the organ, small parenchymal clusters will remain centered around the spread-out terminal branches of the ducts. Here the zonal arrangement of the cells with respect to circulation, function and pathology proves to us, in spite of the doubts of some authors,[46] that lobulation is an essential structural feature of the hepatic parenchyma.

Hepatic lobules were described already by Malpighi[121] in 1666, and Mascagni[125] represented them as grapelike bunches attached to the extremities of the portal vein. A more definite concept of hepatic lobulation was introduced by Francis Kiernan in 1833.[89] He described the hexagonal lobule centered around the radicles of the hepatic veins. This lobule is still presented by the textbooks of histology as the ultimate unit of the liver. However, the idea of a parenchymal mass filling a hexagonal space around the central vein does not integrate functional unity, either normal or abnormal. Therefore, the existence of a hexagonal lobule has been questioned by many authors.[153, 120, 5, 183, 45, 46, 149, 150] In spite of its arrangement within a vascular framework, the hexagonal lobule is not conspicuous under microscopic observation of the hepatic circulation in vivo. The blood flowing through the pairs of terminal afferent vessels streams into sinusoids of an area extending into *sectors only* of adjacent hexagonal fields.[91] Thus it seems that these terminal afferent vessels accompanied by a terminal bile ductule are the orientating landmarks around which the parenchymal tissue

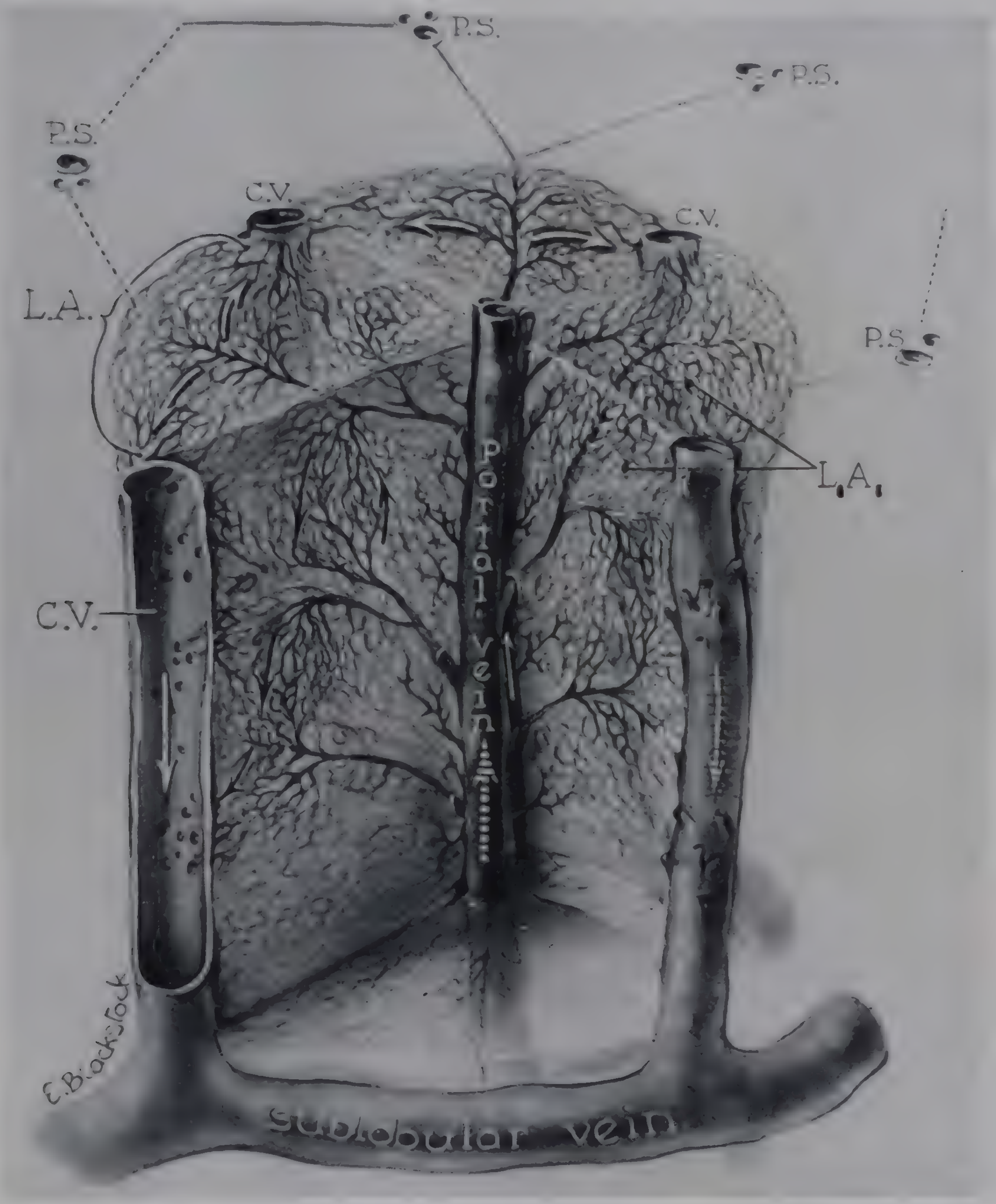


FIG. 5. The vascular architecture of the liver in its relation to the acinar unit. The longitudinal aspect of a small portal space and its component structures are exposed. For simplification only terminal portal branches growing out from the portal vein in this space are drawn. The blood coming up in the portal and the arterial vessels supplies the hepatic units of several hexagonal fields. Note the arcuate courses of the terminal portal branches that follow the axes of the irregularly arranged structural units (LA; L_1A_1). There are many anastomotic pathways, permitting the flow of blood in all directions. Short portal venules are seen, providing a cuff of parenchyma along and around the portal space. L.A. = liver acinus. L_1A_1 = acinar unit penetrating a hexagonal field which is situated well above the level of its origin. P.S. = small portal space or canal. C.V. = central vein. (Rappaport, A. M., Borowy, Z. J., Lougheed, W. M., and Lotto, W. N.: Anat. Rec. 119:11)

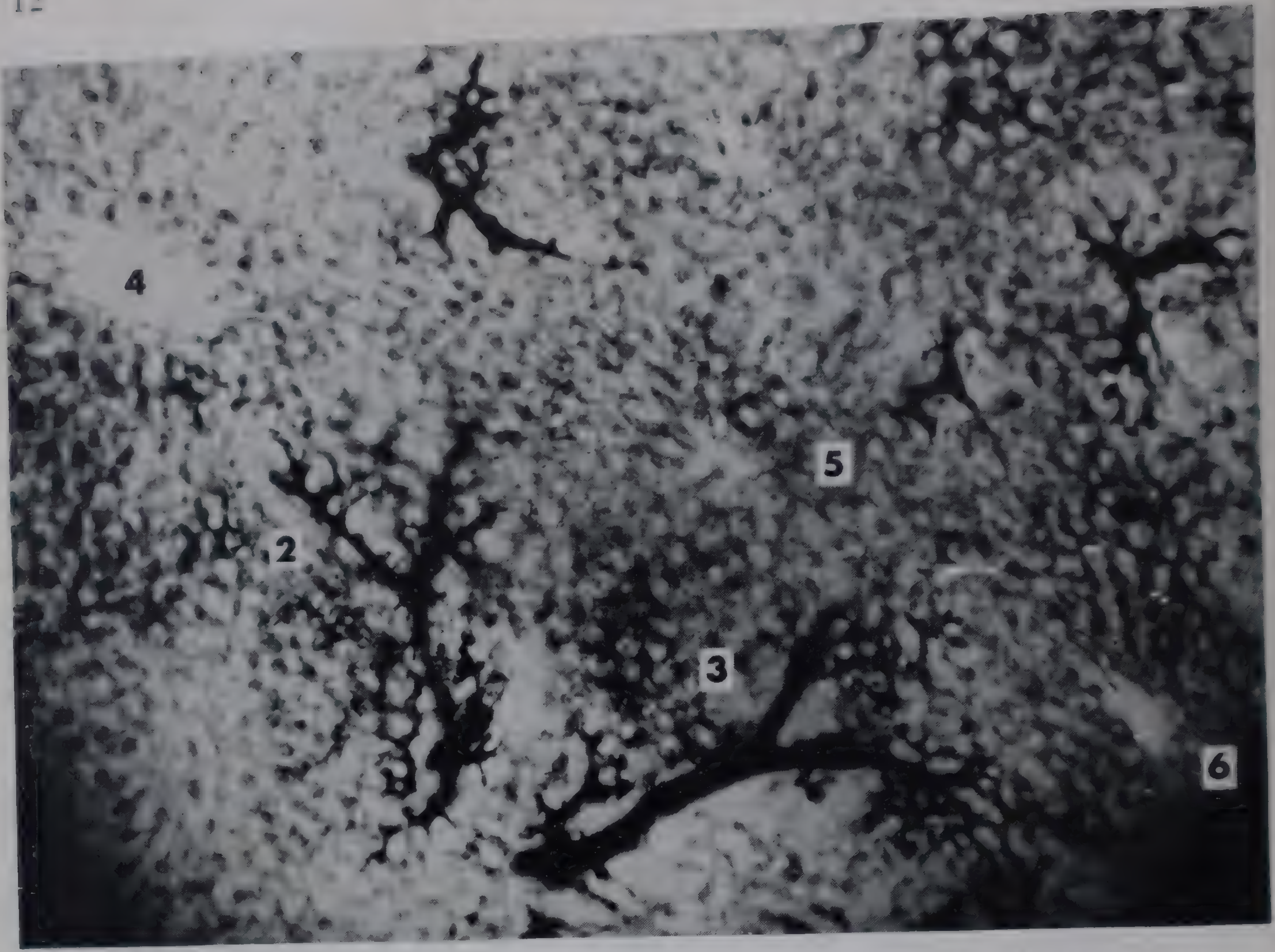


FIG. 6. The interdigitation of portal and hepatic vein branches. Two horizontal terminal portal branches (2, 3), forming the axes of acini, interdigitate with 3 vertical radicles of (central) hepatic veins (4, 5, 6) around which they arch. (Human liver injected with India ink; cleared thick section × 110)

is arranged in clumps or small clusters which, under suitable conditions, can be well delimited.

Two differently colored gelatin masses of the same viscosity injected simultaneously and under the same pressure into the 2 branches of the portal vein of a dog or a rabbit sharply delimit parts of the liver. Microscopically, differently colored areas are found to be situated around terminal portal branches, to occupy adjacent parts of neighboring hexagonal fields and to extend from the central vein of one hexagon to the central vein of another (Fig. 3). The same arrangement is observed when the colored masses are injected into the 2 branches of the hepatic artery or bile duct. Thus the hexagonal fields are broken down into distinct areas that are the cross sections of berrylike **irregular** parenchymal masses surrounding a trio of axial channels. Of these the hepatic arteriole and the portal venule bring in the materials for metabolism while the accompanying terminal bile ductule carries away the product of secretion. Each of these outlined parenchymal masses represents the hepatic structural and functional unit, which we named the liver acinus. It is defined as *the small* **irregular** *berrylike parenchymal mass situated around the trio of terminal branches of portal vein, hepatic artery and bile duct growing out from a small portal space and running mainly perpendicular to the central veins with which they interdigitate.*[150] (Fig. 4 A, Fig. 6.) These *simple acini* are part of *complex acini,* which in turn are parts of *acinar agglomerates*. The complex acini represent the parenchymal clumps around a preterminal trio of channels and their terminations (Fig. 9 B). While the axial structures of the complex acini run perpendicular to the central veins, their offshoots do not

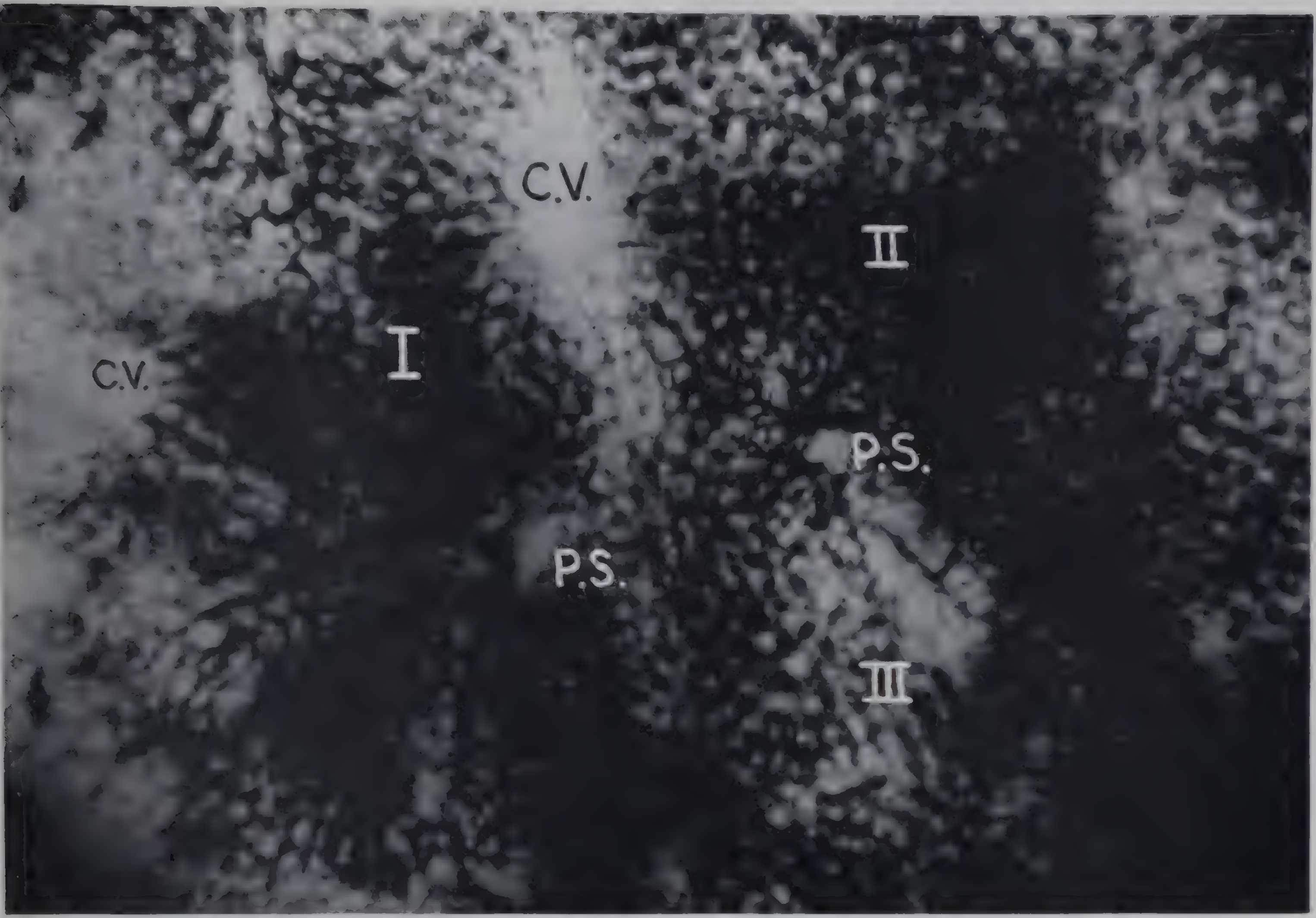


FIG. 7. The acinar units and the hexagonal field. The tissue around a central vein (C.V., near center of upper half of the field) is composed of parts of acini (e.g., I, II and III) which form the lower half of a hexagonal field. Their ink-filled axial vessels grow out from two small portal spaces (P.S., P.S.). The tissue of the upper part of this field stems from other acinar units. Acinus I is seen to be drained by two "central" veins (C.V., c.v.). (Human liver injected with India ink; cleared thick section × 110)

follow this rule rigidly. The *acinar agglomerates* are situated around large portal arterial and bile channels. Developmentally, however, the simple acini and their axial structures are outcroppings of a preterminal bile duct and associated vessels which form the axis of a complex acinus just as complex acini are offshoots of acinar agglomerates. In addition, there are, around and close to the portal spaces, simple acini and sometimes complex acini, the axial structures of which arise directly from large conducting channels in the spaces. These acini take part in the formation of the cuff of parenchyma that continuously envelops the portal canals. In the human liver the acini (Fig. 4 A) and the acinar agglomerates (Fig. 4 B) become evident when India ink is injected under a pressure of 10 mm.Hg into the portal vein.

The architectural framework of the liver acini is represented by the afferent vascular trees, closely followed in their branchings by the bile ducts and ductules as illustrated in Fig. 5. The blood coming up through the portal space with the respiratory tides in the portal branch and with pulsating jets in the arterial channel disperses like a fountain through their terminal afferent twigs and sinusoids; it waters and nourishes the parenchyma of the liver acinus, extending into several adjacent hexagonal fields. The bile secreted by this structural unit and collected in the bile capillaries is drained by the terminal bile ductule and duct accompanying the afferent vascular channels. The latter, and consequently the liver acini, have by no means a rigid geometric arrangement around the central veins; they run in curved rather than straight lines but mainly perpendicu-

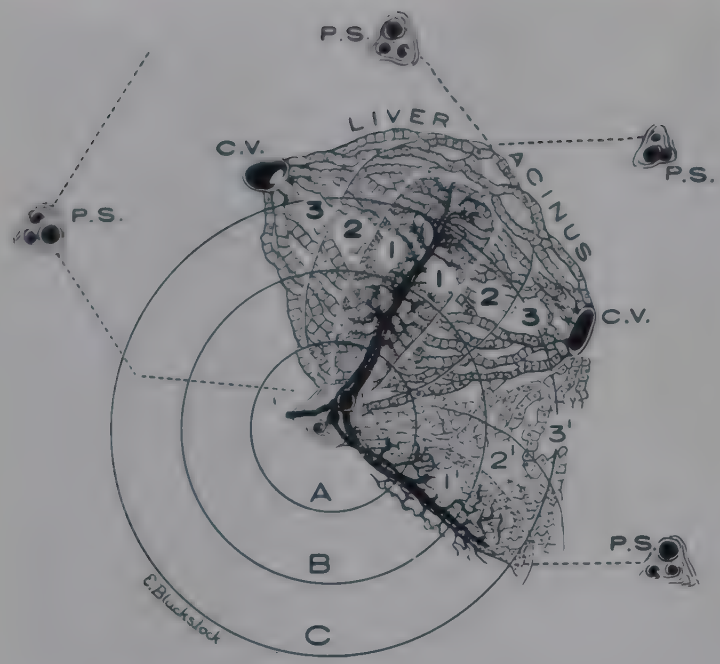


FIG. 8. The blood supply of the hepatic acinar unit. The liver acinus occupies adjacent sectors of neighboring hexagonal fields. Zones 1, 2 and 3 respectively represent areas supplied with blood of first, second and third quality with regard to oxygen and nutrients. These zones center about the terminal afferent vascular branches and extend into the portal field from which these branches originate. Zone 1', 2' and 3' designate corresponding areas in a portion of an adjacent acinar unit. In Zone 1 and 1' the afferent vascular twigs empty into the sinusoids. The circles A, B and C delimit concentric bands of hepatic parenchyma around a small portal field. They mark the circulatory zones in decreasing order of nutrients and oxygen content as assumed in the classical concept of hexagonal units. (Rappaport, A. M., Borowy, Z. J., Lougheed, W. M., and Lotto, W. N.: Anat. Rec. **119**:11)

lar to the terminal hepatic (central) veins with which they interdigitate. This relationship between the microscopic afferent and efferent hepatic vessels (Fig. 6) is the same as that observed in the gross specimens where the interdigitating course of the intrahepatic vessels is brought out clearly by injection and corrosion procedures.[44, 48]

The various ways of branching and anastomosing of the terminal afferent vessels with vascular areas situated above and below a hexagonal field indicate that the hepatic structural units (acini) are connected intimately with each other (Fig. 5). However, each of them is centered definitely around its main axial bile and vascular channels. This centering can be seen readily in Figure 7, a cleared thick section of a human liver, injected with India ink. The cluster of parenchyma is outlined distinctly by the well-filled thicket of sinusoids that extends between the central veins of 2 neighboring hexagonal fields.

The hexagonal pattern in the hepatic parenchyma that has fascinated the histologists for about 100 years is seen to be the result of tridimensional budding of the terminal bile ducts and accumulation of connective tissue around them.[149, 150] While some authors[153, 120, 45, 46] deny the existence of the hexagonal lobule, others [131, 104] consider it as a structural unit which, because of its arrangement around a central vein, is most adequate for metabolic activity. But metabolic as well as endocrine exchange takes place in the sinusoidal glomus and not in the peripheral veins that drain the capillary network. In the acinar concept the sinusoids cease to be a random network of capillaries. They form the well-delimited (Fig. 7, I, II) and distensible framework of a small parenchymal unit which they sustain and supply completely. Sinusoids are arranged as radial and peripheral channels[45] and are orientated after venules and arterioles, the offsprings of acinar axial vessels.

A zonal relationship between hepatic cells and their blood supply derives from this acinar concept. The liver cells situated close to the axial vascular twigs (Fig. 8, Zone 1) are the first to be supplied with blood rich in oxygen and nutrients. The more distant the parenchymal cells are from the site where the terminal afferent vascular twigs empty into the sinusoids, the poorer the quality of blood that bathes them and the less their resistance to damage (Zones 2 and 3). It is evident that all cells lying in the areas concentric about the portal space do not share equally the possibility of being supplied with fresh blood. Some cells in area B or C (Fig. 8), farther from the portal field, will have an excellent blood supply from the terminal vascular twigs branching out from the same portal space. Some cells in area A, although close to the vascular chan-

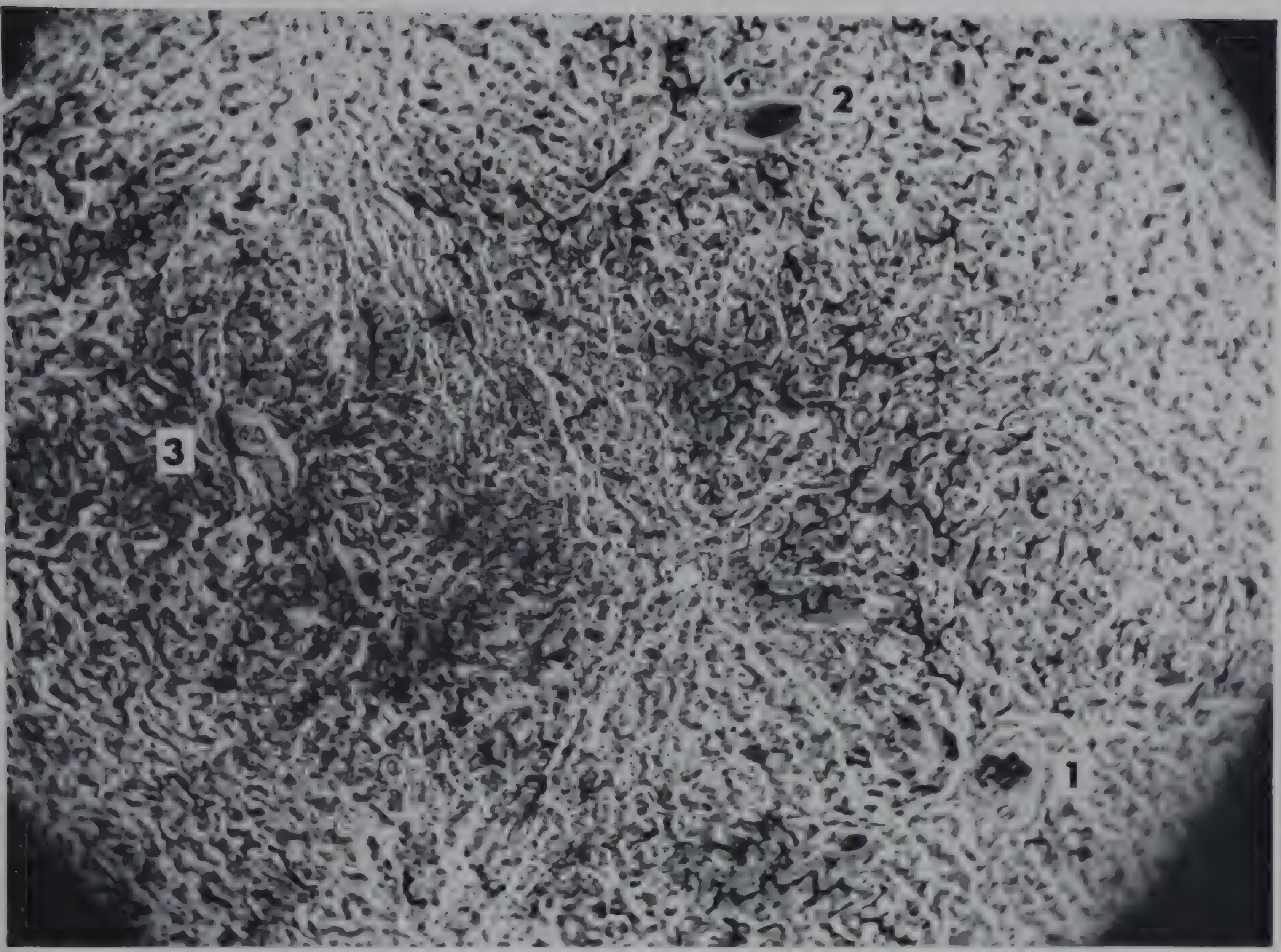


FIG. 9 A. The breakdown of the uniform parenchymal mass into its acinar constituents. Ischemic necrosis developing and progressing along the periphery of the acinar units delineates their boundaries. Note the 3 portal spaces (1, 2, 3) situated in the 3 corners of the field and arranged almost equidistantly on a circle surrounding the central vein. Note also the irregular acini (injected with India ink) that grow out from the portal spaces, and a small ink-filled venule leaving space 3. The "central" necrosis has stellate shape, and its projections extend toward and beyond the weakest points of circulation, the site where the capillarized tips of the acini meet each other. A similar distribution of lesions is observed in fatty change and in dietary cirrhosis.

nels of the portal triad, are at a disadvantage with regard to oxygen and nutrients because they are remote from the terminal afferent arterioles and portal venules. However, other cells in the same area, as can be seen in serial sections of the liver, are supplied by small inlet venules or by axial vessels of simple acini that branch off directly from the larger conducting portal branches. Similar vessels were described by Daniel and Prichard in 1951.[34]

The zonal arrangement of the parenchymal cells around the axial channels sustains the dynamic concept of synergetic structural elements that are united by blood supply and function, and a better understanding of the metabolic cell activities is made possible. In starvation, for instance, the cells close to the axial vessels will become depleted of their basophilic material early.[97] However, fat will be brought from the fat depots into the liver by the incoming vessels and therefore will be found unloaded in Zone 1 (Fig. 8).

The anatomy of pathologic processes, such as ischemic necrosis, early fatty change[76] and early dietary cirrhosis,[70] is now easier to explain. Such processes initiate changes in Zone 3 (Fig. 8) at the circulatory periphery of the acinar units, which thereby become outlined and conspicuous. Serial sections of a specimen presenting ischemic necrosis and injected with India ink through the portal

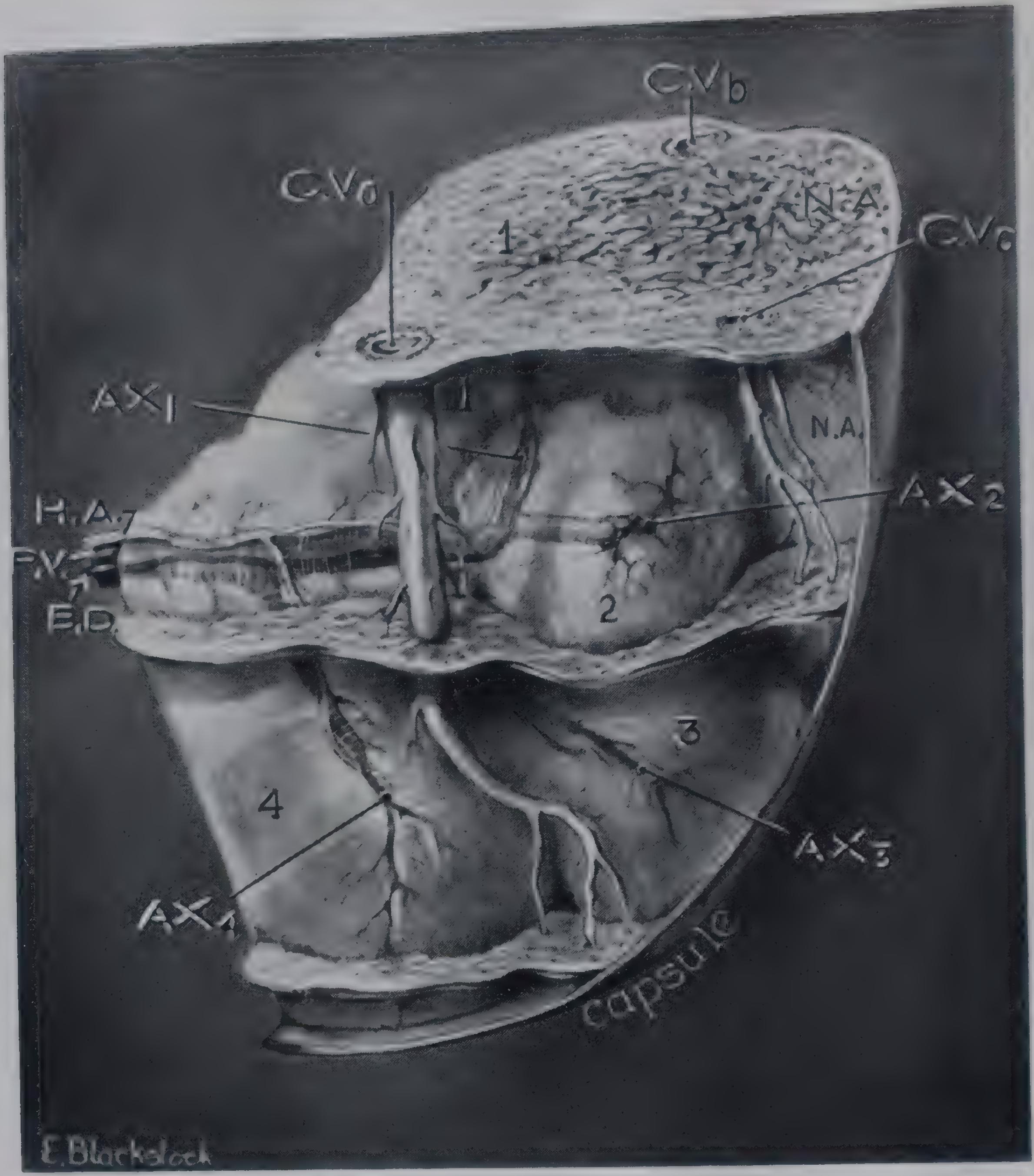


FIG. 9 B. Complex liver acinus. (Tridimensional reconstruction after 150 serial sections, each 5 μ thick. The unity of parenchyma was disrupted by a mild ischemic necrosis induced at the circulatory periphery of the acini. India ink was injected through the portal vein in order to outline the terminal afferent vessels and sinusoids of the surviving parenchymal clumps. These are represented as if they had been peeled out of their necrotic outskirts. The amount of necrosis induced can be judged by the three shelves, the remnants of necrotic tissue that surrounded the central veins and involved the circulatory periphery of the acini.)

This complex acinus lies beneath the hepatic capsule.

H.A., P.V. and B.D. = hepatic artery, portal vein and bile duct forming together the axis of the complex acinus and running perpendicular to the central veins (CV_a, CV_b and CV_c).

AX_1, AX_2, AX_3 and AX_4 = the trios of terminal branches of H. A., PV. and B.D., each of them forming the axis of a corresponding simple acinus (1, 2, 3, 4).

AX_4 and AX_3 course perpendicular to CV_a.

AX_2 lies perpendicular to CV_a and CV_c.

AX_1 runs obliquely to CV_a and CV_b.

N.A. = section of a neighboring acinus growing down from above and lying beneath the hepatic capsule. Most of the India ink seen in the plane of section stems from the injected axial vessel of N.A. There is no axial vessel visible in the sectioned tip of acinus 1.

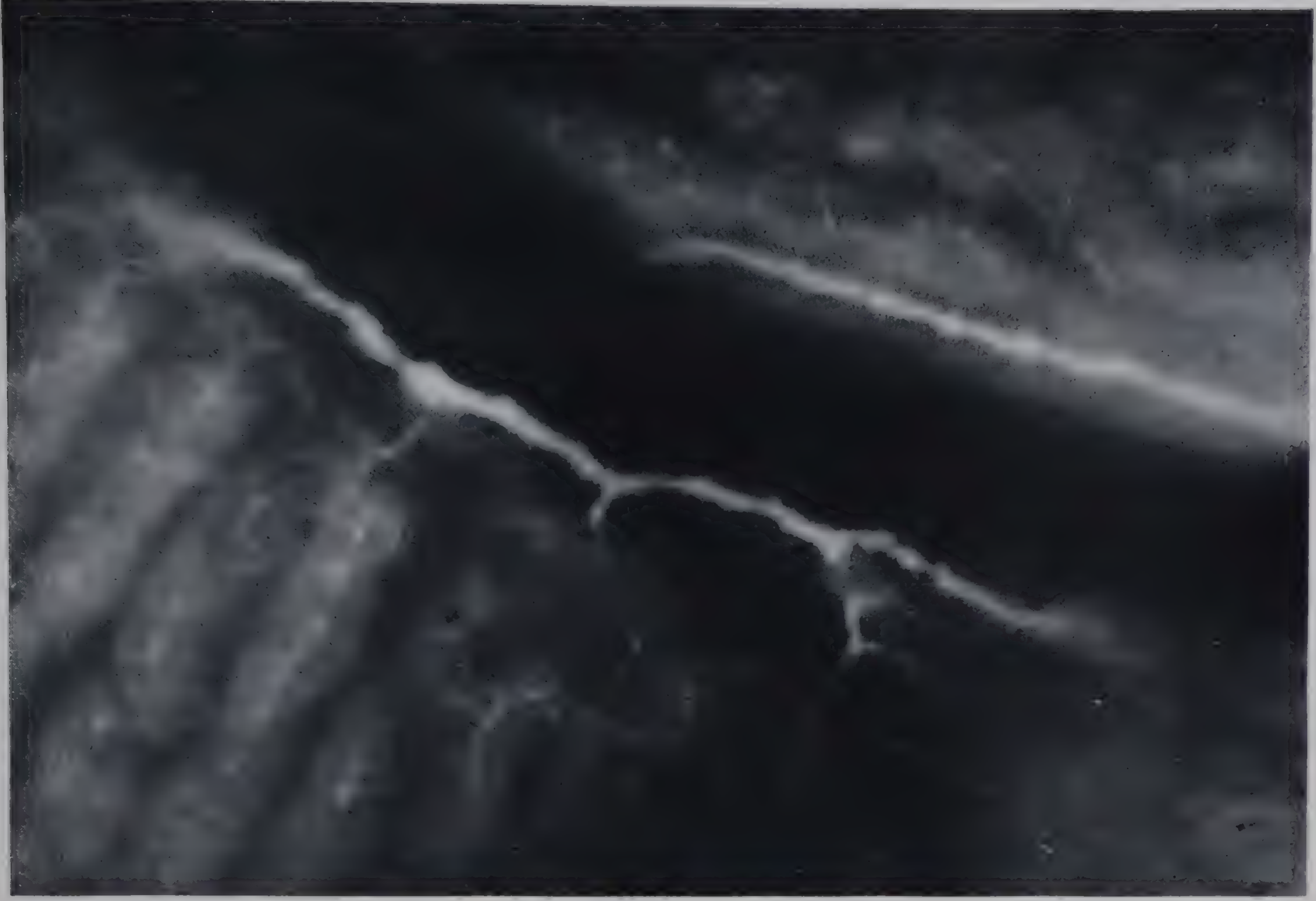


FIG. 10. Uranin secretion of the liver cells in a rat. The uranin content of the bile makes visible the bile canaliculi, the intermediate canal of Hering (left upper corner) and the terminal (axial) bile ductules. The latter accompany a terminal (axial) portal branch which courses close to the liver surface. × 500 approx. (Hanzon, V., and Blomqvist, B.: Anatomiska Institutionen, Uppsala, Sweden)

vein reveal the acini, their thickness (about 2 mm.) and their irregularity (Fig. 9 A). A tridimensional representation of a complex acinus delineated by ischemic necrosis and reconstructed from 150 serial sections and serial microphotos, is seen in Fig. 9 B.

As soon as one ceases to consider as a uniform structural mass the tissue contained in a hexagonal field, it becomes evident that pathologic changes observed in one hexagonal field are not necessarily those of one structural unit. This concept permits a rational approach to the thorny problem of focal and zonal necrosis. The lesions observed in a hexagonal field may be due to the tangential sectioning of the necrotic periphery of a structural unit that lies above or below the plane of section, the afferent vessels of which may have suffered from ischemia.

Structural Elements of the Hepatic Units

1. HEPATIC CORDS AND PLATES. The oversimplified description of a test-tubelike hepatic epithelium arranged in cords, 2 cells thick and comprising a bile canaliculus between them,[116, 117] has been revised by Elias' tridimensional studies of the mammalian liver.[44, 45, 47] The parenchyma of the human liver is fashioned in cribriform sheets or plates 1 cell thick. Each cell is surrounded by a polygonal network of bile capillaries which unite in the bile canaliculi. This concept leans on earlier observations of Koelliker (1853),[93] Hering (1872),[73] Braus[19] and Pfuhl.[139] Perhaps it can be challenged by the observations made with intravital fluorescence microscopy.[68] Also, in random sections hepatic cells in sheet arrangement are observed rarely. However, the acinar arrangement of sheets and plates, resulting from the fusion of branched cords that surround axial channels and are situated perpendicularly to

the central veins, explains why we find unicellular chains of cells rather than sheets or cords.[150]

2. Bile Capillaries, Canaliculi, Intermediate Canals of Hering[73] and (Axial) Terminal Bile Duct Branches. The study of the bile capillaries has reached safer ground since Ellinger and Hirt[49] first visualized by fluorescence microscopy the bile capillaries in vivo. However, it is to the credit of Grafflin and associates[59] that they recognized certain phenomena in this capillary pattern as abnormal. These phenomena were brought about by abnormal conditions inherent in the method and the prolonged observation. V. Hanzon[68] too has proved that a capillary plexus surrounds each liver cell in a lamina except for the side exposed to the sinusoids. Bile capillaries empty into bile canaliculi, which in their zigzag course reach the intermediate canal of Hering (Fig. 10). It was confirmed by electron microscopy[18] that the walls of the capillaries and the canaliculi are formed by the modified membranes of the surrounding hepatic cells (Fig. 2). The intermediate canal, *Zwischenstück* of Hering, was reinvestigated by Clara.[26] Its wall is composed of cuboidal to flat epithelial cells containing a dark-staining argentophilic nucleus. Its length is from 3 to 4 cells, and at its junction with the bile canaliculus there is an ampullalike dilation of its lumen.[50] Several intermediate canals join the axial terminal branch of the bile duct. The region of the canal of Hering is richly vascularized and it is the site of parenchymal repair and perhaps of fluid absorption.

3. Terminal (Axial) Branches of Afferent Vessels. Sinusoids. Radicles of Hepatic Veins

A. *Portal vein.* H. Elias[45] introduced a distinctive nomenclature for the finer intrahepatic ramifications of the portal vein. His differentiation into "conducting" and "axial distributing veins," although possible only when these vessels are seen cut longitudinally, is very suitable for practical purposes. However, serial sections of conducting veins will reveal the regular branching out of venules to supply a periportal cuff of tissue. Thus the "conducting veins" distribute blood quite regularly to neighboring tissue too Similar observations were made by Daniel and Prichard.[34] In distinction, however, the "axial distributing vein"[45] is a terminal branch of the portal vein and usually is situated in the axis of an acinar unit, the sinusoidal glomus of which it supplies with its arborizing inlet venules. These venules show sphincter activity that regulates the amount of portal blood in the sinusoids.[92] The histologic features of these sphincters are not described fully.

B. *Hepatic artery.* The hepatic artery supplies all the structures in the portal tracts and also the sinusoids. Its terminal ramifications have been the object of many studies and still are debated vividly.[46] There are great differences of opinion as to the actual arterial terminations and the way they join the portal vein. Indeed, two blood streams flow into a firmly encapsulated organ, the arterial under pressure of 120 mm.Hg, the portal under 9 mm.Hg. The question as to how the portal blood streams uphill still is not answered fully. We believe that sluice mechanisms can raise the one stream to the level of the other by means of sphincters at the junction of arterioles and arterial capillaries with portal venules and sinusoids. There are also sphincters at the outlets of the sinusoids into the peripheral veins. Sphincter activity has been observed by several workers,[92, 156, 170] but the information about the histologic features of these sphincters is very recent,[31, 45] and they have not yet been investigated completely.

According to Hale's[66] clear review, the distribution of the terminal (axial) branches of the hepatic artery may be divided into (a) a general plexus within the portal tract, (b) a special capillary plexus surrounding the bile ducts (peribiliary plexus) and (c) the arterial capillaries emptying directly into the sinusoids (Fig. 11).

a. *General plexus* supplies the structures within the portal tract, except for the terminal branches of the bile duct. These capillaries have a more open network woven around the contents of the portal space and send branches into the radial or peripheral sinusoids.[108, 132, 23, 159]

b. *Peribiliary plexus* consists of a close network around the bile ducts up to their terminal branches. These capillaries play an important role in absorption and concentration of bile, in regeneration of hepatic parenchyma and in collateral arterial circulation of the hepatic parenchyma[151] (pp. 27, 33). Branches of this plexus pass into radial[132, 8] and peripheral[4, 45] sinusoids and through capillary connections join the portal vein. These capillaries form the so-called "internal radicles of the portal vein."[89, 29, 108, 23, 8, 4] Another connection between arterioles of this plexus and venules of the portal vein, provided with sphincters that are important for raising the pressure and speeding the flow in the portal venules, has been observed by earlier workers.[81] It has found its confirmation through microscopic observation of the intrahepatic circulation in vivo.[92, 170]

c. *Arterial Capillaries Emptying Directly into Sinusoids.* The intralobular arterial capillary running freely through the hepatic parenchyma was described by earlier workers[25, 19] and again by recent investigators.[45, 46, 156] However, the zone in which it lies and its mode of termination never have been described exactly.

In *summarizing,* we must say that the

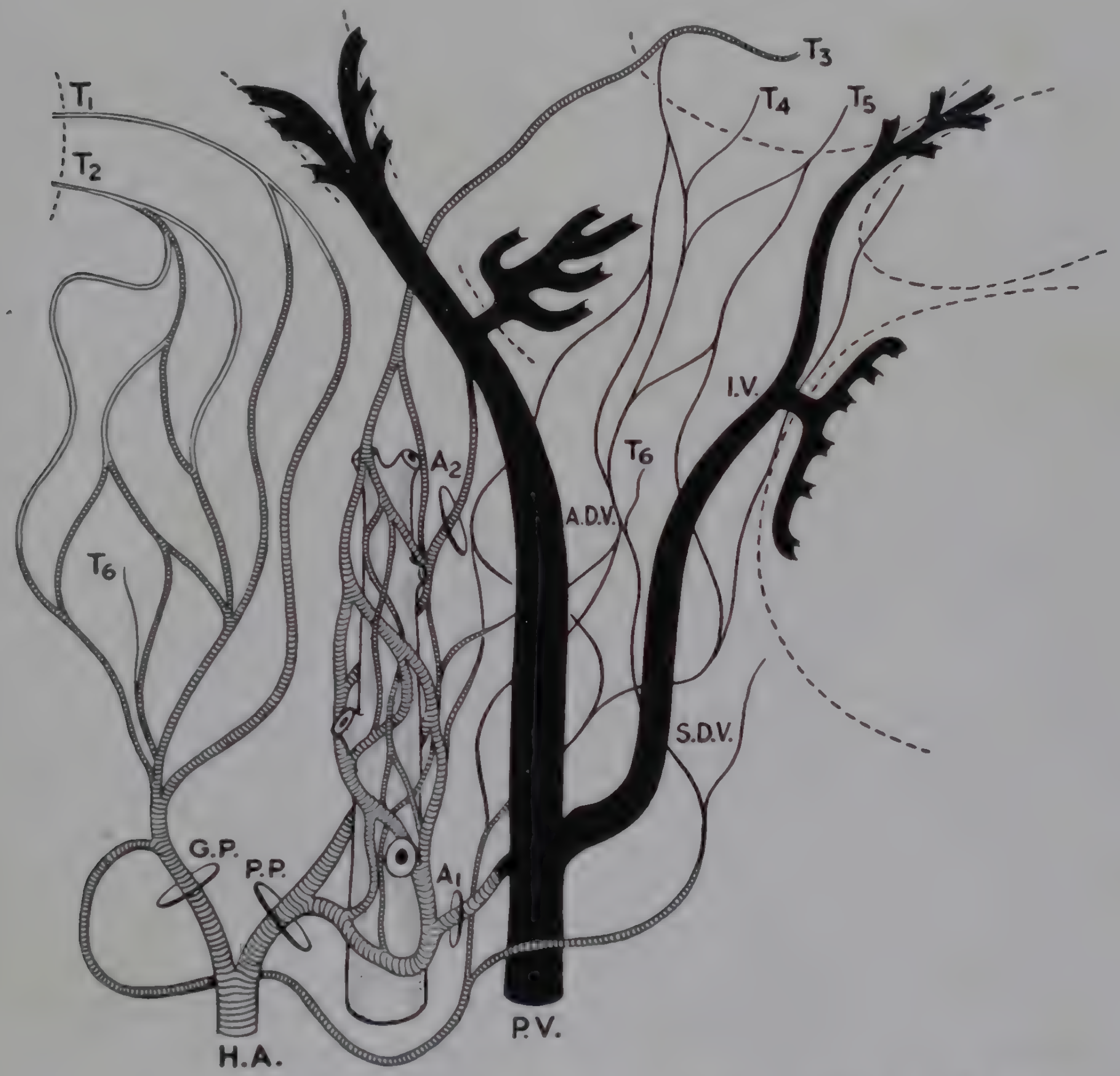


FIG. 11. H.A. (hepatic artery). G.P. (general plexus of the hepatic artery). P.P. (peribiliary plexus of the hepatic artery). T_1 (branch from general plexus, emptying into a radial sinusoid). T_2 (branch from general plexus, emptying into the peripheral sinusoid). T_3 (intralobular capillary). T_4 (branch from peribiliary plexus, emptying into a radial sinusoid). T_5 (branch from peribiliary plexus, emptying into a peripheral sinusoid). T_6 (branch from either plexus, terminating in the tissues of the portal tract). P.V. (portal vein). A.D.V. (axial distributing vein). S.D.V. (small distributing vein). I.V. (inlet venule). A_1 (arteriolar-venular anastomosis between hepatic artery and portal vein). A_2 (capillary anastomosis between hepatic artery and portal vein). Stippled area represents bile ducts. Interrupted lines represent the limits of hexagonal fields. (Hale, A. J.: Glasgow M. J. 32:283-301)

structural complexity of the arterioportal junctions adds to the difficulty of exact understanding of the mechanism of the dual blood supply. However, precise knowledge of the intrahepatic circulation is essential for the solution of many problems of hepatic physiology, pathology and therapy.

C. *Sinusoids.* Those who consider the aspect of narrow islets of cells between wide capillary canals as being brought about by the penetration of solid parenchymal masses into the omphalomesenteric lakes may regard the rows of epithelial cells in a microscopic field as the sectioned tips of coral formations whose narrow walls crisscross down deep to the bottom of the lakes, forming a labyrinthine scenery.

Those who are inclined to see in the architecture of the liver lobule the stamp of endocrine rather than exocrine activity[131, 104] are supported in their opinion by the close relationship between parenchyma and capillary glomus, and by the structure of the sinusoids, but not by their radial course toward the radicles of the hepatic veins. Indeed, as in other endocrine organs, rows of parenchymal cells are bordered by large capillaries into which metabolic products and waste are poured. But, endocrine organs, e.g., adrenal and pituitary, show neither radial capillary course nor central veins to drain them. Furthermore, the hepatic capillaries are unique in their thin endothelial syncytial lining and their large von Kupffer cells.[95, 92, 168] These phagocytic endocytes[176] are attached to the endothelial plasmodium and spread their stellate processes through the capillary lumen toward different points of the wall where they anchor.[174] Besides their role in the production of bilirubin, they are the scavengers of this complex canal system, clearing it of particulate matter, old erythrocytes, bacteria[123] and debris which they engulf.

The width of the sinusoids varies from 6 to 30 μ, and can increase to 180 μ when necessary. This change in caliber is due to contractility, an exquisite feature of these capillaries, the structural elements of which are not yet investigated fully. There is also tonic contractility[92] which, together with the inlet and the outlet sphincters (p. 18) helps to regulate the amount of flow through a vascular area. The activity in the sinusoids is intermittent. Groups of sinusoids shift their work asynchronously. The circulatory activity spreads simultaneously to those sectors of neighboring hexagonal fields that are adjacent to the active axial vessel.[91] This phenomenon explains itself as circulatory activity of single acini (Fig. 7, I, II). About 25 per cent of sinusoids are active while the remainder are resting or storing blood.[170] Thus is disclosed the microscopic feature of the function of the liver as a "venesector and blood giver of the circulatory system."[86]

D. *Radicles of the Hepatic Veins.* The histologic feature of the junction of the sinusoids with the hepatic veins where sphincter activity is observed in vivo needs further investigation.[149] Also, the abrupt transition from capillaries to such large vessels as the central veins is unusual in vascular anatomy. Whether the majority of the sinusoids empty individually or through collecting venules into the radicles of the hepatic veins also has not been determined yet. However, Hanzon's microphotos[68] of the different phases of the uranin secretion in vivo, his Figures 16 and 39, demonstrate that different acini around a central vein empty into collecting venules which they border. The central veins are the drainage centers of several collecting venules as well as of individual sinusoids. The sluice channels of Deysach[37] are collecting venules surrounded by sphincters at their site of junction with the sublobular veins into which they shortcircuit a certain amount of sinusoidal blood when needed. The radicles of the hepatic veins represent the drainage centers into which peripheral and radial sinusoids of different acini empty their blood (Fig. 4). The absence of a limiting plate around these veins also indicates that the surrounding tissue is not bound together and lacks unity. Therefore, an area of early necrosis around the central veins produced by hepatic ischemia has a stellate shape. Its processes are arranged radially and delimit the periphery of the individual acini of which the central veins are the efferent channels.[150] The walls of the hepatic veins have also contractile sphincters. In dogs the smooth muscles in the wall of the hepatic veins contract during shock.[126] The presence of these muscle fibers in dogs and humans has been described by early workers[20] and later demonstrated by

Popper,[143] who found that an inversely proportional rate of flow is possible in the hepatic veins and their mural lymphatics.

The interdigitating relationship between the channels of the hepatic vein and the portal vein observed in the gross specimen is maintained in the microscopic field between terminal branches of these veins. The terminal (axial) branches of the portal vein and the hepatic artery run perpendicular to the radicles of the hepatic veins which they surround.

Summary: The essential feature of the hepatic parenchyma is its lobulation. It is not a matter of conjecture but a biologic principle that secreting cells have a definite arrangement around the very small afferent vessels on which their function and nutrition depend. They also have an intimate connection with the very small excretory channels through which their products are discharged. This principle is depicted in the liver acinus, the above-described hepatic structural and functional unit. It can be demonstrated by special injection technic and also is revealed in the pattern of certain pathologic processes.

THE VESSELS OF THE LIVER

A. EXTRAHEPATIC DISTRIBUTION OF THE HEPATIC VESSELS

The liver receives blood through the portal vein and through the hepatic artery, a branch of the celiac axis. As the portal vein drains the blood of an area supplied by the other branches of the celiac axis and by the superior and the inferior mesenteric arteries, the amount of blood flowing into the liver depends in fact on the flow in these arteries.

Common Hepatic Artery. This artery, the second major branch of the celiac axis, courses to the right along the upper border of the pancreas in the right gastropancreatic fold, which conducts the artery to the medial border of the hepatoduodenal part of the lesser omentum. It ascends in front of the portal vein and to the left of the bile duct. It divides into the left and the right hepatic arteries to supply the corresponding lobes of the liver. Michels[127] sees the hepatic artery dividing into 3 terminal branches: right, middle (for quadrate lobe) and left. There is an extensive literature on the anomalies of the hepatic artery and its branches. This subject has been dealt with recently by N. A. Michels[127] and by E. V. Johnston and B. J. Anson.[85] We shall mention the common anomalies and their relationships to the ducts.

ANOMALIES OF THE HEPATIC ARTERY. In about 50 per cent of cases, there are aberrant hepatic arteries. The right hepatic artery springs from the superior mesenteric artery, while the left aberrant hepatic artery derives frequently from the left gastric artery. Each of these arteries is often the single hepatic artery, and its injury can damage the liver severely. An unusual combination of several aberrant hepatic arteries was recently reported by C. P. Mills.[128]

As the cystic artery (surgically important)

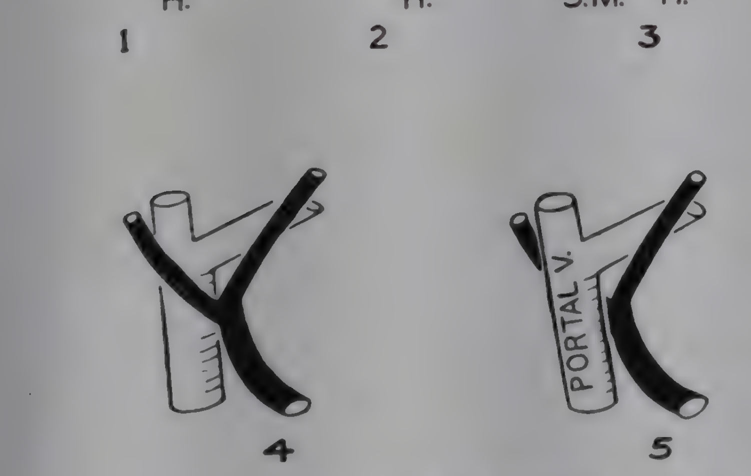


FIG. 12. Anomalies of hepatic artery. Their relation to portal vein and bile duct.

1. Anterior to the bile duct, 24%
3. Posterior to the bile duct, 64% } 100%
3. Arising from superior mesenteric artery, 12%
4. Anterior to the portal vein, 91% } 100%
5. Posterior to the portal vein, 9%

R.H. = Right hepatic artery; L.H. = Left hepatic artery; S.M. = Superior mesenteric artery. (Grant, J. C. B.: Method of Anatomy, ed. 5, Baltimore, Williams & Wilkins) arises in about 35 per cent of the cases from the right hepatic branch only, or from a right hepatic artery, the variations and the topographic relationship of these arteries with the bile duct and the portal vein are important (Fig. 12).

Cystic Artery. The cystic artery arises in about a third of the cases from the right hepatic artery in the upper part of Calot's triangle formed by cystic and hepatic duct and therefore has the above relationship to bile duct and portal vein as indicated in Figure 12 (for other variations see Daseler & assoc., 1947).[35] The cystic artery divides into a superficial branch that is distributed to the peritoneal surface of the gallbladder and a deep branch supplying the attached wall of gallbladder and its bed. The artery is single in 75 per cent of cases and double in 25 per cent. In the latter, the deep and the superficial branches have each a separate origin.

Terminal Branches of the Hepatic Artery. These vessels enter the portal fissure and lie here in a plane between the bile ducts and the branches of the portal vein which they flank to the left. Left and right arterial trunks anastomose rarely outside the portal fissure but intercommunicate by smaller twigs present in the deeper folds of the capsule of Glisson within the groove of the round ligament.[58] This explains why, after ligation of one branch of the hepatic artery in the autopsy specimen, the entire liver still can be injected with a barium mass through the other arterial branch.[155] Inside the liver substance the terminal branches of the hepatic artery communicate with each other and the portal vein only through capillaries. The ramifying gastroduodenal and right hepatic arteries, branches of the proper hepatic artery, are of importance as potential collaterals to the liver.

Portal Vein. The valveless portal vein is an afferent nutrient vessel of the liver, and in this sense is an arterial channel. It carries blood from the entire capillary system of the digestive tract, the spleen, the pancreas and the gallbladder.

The portal vein derives from the omphalomesenteric veins which bring blood from the yolk sac and the intestines to the liver. The omphalic portion of these veins regresses with the disappearance of the yolk sac. With the growth of the intestines the mesenteric portions persist and become the tributaries of the portal vein. Its stem is formed by the omphalomesenteric trunks arranged in a figure-of-8 around the first and the third portions of the duodenum. Its spiral course is formed by dropping out the posterior (right) limb of the "8" below and the anterior (left) limb of the "8" above.

ANOMALIES OF THE PORTAL VEIN. These variations are rare. The cavernomatous transformation of the portal vein is considered by some authors as an acquired anatomic anomaly due to early thrombosis and recanalization of the portal system.[162] Others consider it as an atypical development of the plexus of veins between the omphalomesenteric and the hepatic veins during the second months of fetal life.[54, 12]

Of recent years more frequent operations on the portal vein have led to new investigations of its anatomy.[40, 145, 57] It has been found constant in its length but extremely variable in its tributaries.

Splenic Vein. This vein (0.43 cm. diam.) commences with 5 to 6 branches that return the blood from the spleen and unite to form a single nontortuous vessel. In its course across the posterior abdominal wall it grooves the upper part of the pancreas, from which it collects numerous short tributaries. It can be visualized preoperatively by splenoportography.[1, 7, 100] It runs close to the hilum of the left kidney and terminates behind the neck of the pancreas, where it joins at a right angle the superior mesenteric vein. Because of its nearness to the vessels of the left kidney the splenic vein can be anastomosed to the renal vein. Its tributaries are the short gastric veins, the pancreatic veins, the left gastro-epiploic vein and the inferior mesenteric vein.

Inferior Mesenteric Vein. This vein (0.24 cm. diam.) returns blood from the area irrigated by the superior and the inferior left colic and superior rectal veins.

Superior Mesenteric Vein. This vein (0.78 cm. diam.) is second in diameter to the portal vein itself and well suited for anastomosis with the caval system. It carries blood from the veins of the small intestine, of the cecum and of the ascending part of the transverse

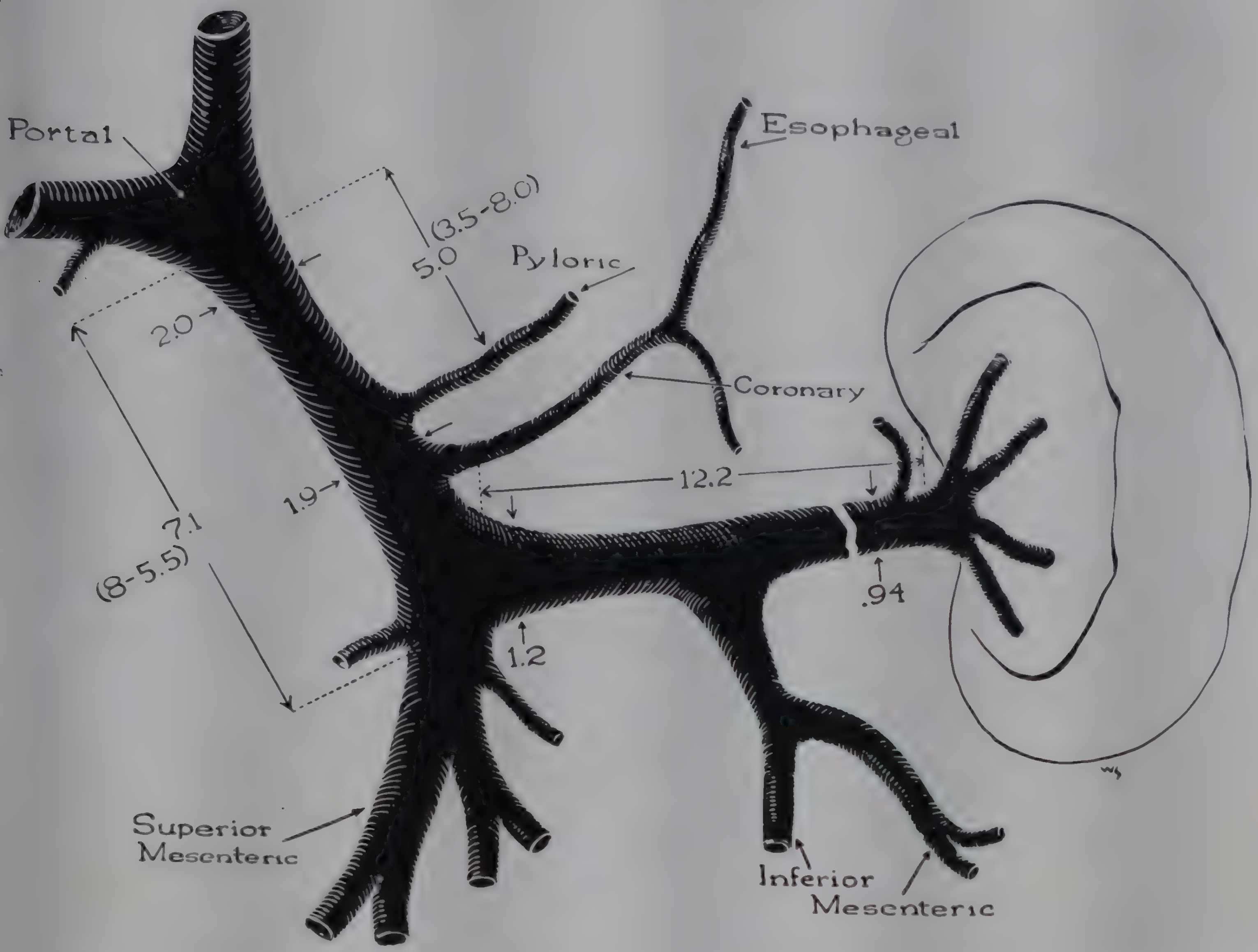


FIG. 13. Mensuration of the portal vein and its main branches. Figures are in centimeters. (Gilfillan, R. S.: Arch. Surg. **61**:449-461)

colon. In its upward course it passes the right ureter and the inferior vena cava, the third part of the duodenum and the uncinate process of the pancreas and unites with the splenic vein and sometimes with the inferior mesenteric vein to form the portal stem. Other tributaries of the superior mesenteric vein are the pancreaticoduodenal veins and the right gastro-epiploic vein.

Portal Stem. The portal stem (around 2 cm. in diam.) is formed behind the neck of the pancreas by the confluence of the splenic and the superior mesenteric veins. The length of the portal stem is approximately 5.5 to 8 cm. (Fig. 13). The portal stem receives the superior pancreaticoduodenal vein, some accessory pancreatic veins,[40] the pyloric vein, the left gastric (coronary) vein and the cystic vein. Usually there is an upper segment of the portal vein, averaging 5 cm. in length, which is devoid of major branches.[57] Here surgical dissection can be started without danger of hemorrhage. The most troublesome tributary of the portal stem is the left gastric (coronary) vein. It runs upward along the lesser curvature of the stomach, where it receives some esophageal veins. With the progressing cirrhosis of the liver these enlarge to form varices that are apt to produce fatal hemorrhage. The portal stem runs in the hepatoduodenal ligament in a plane dorsal to the bile duct and the hepatic artery and divides into 2 branches before entering the portal fissure. The right branch, short and thick, receives the cystic vein. The left branch, longer and smaller, is joined by the umbilical vein (lig. teres) and the associated para-umbilical veins. It connects by the venous ligament (ductus venosus Arantii) with the inferior vena cava. The left portal trunk gives branches to the quadrate lobe and also to the caudate lobe before entering the liver at the left end of the porta hepatis.

B. INTRAHEPATIC DISTRIBUTION OF THE HEPATIC VESSELS

The topography of the vascular and biliary structures within the liver were studied recently by Segall,[155] Hjortsjö[77, 78] and Fainsinger.[51] Elias and Petty[48] and also Couinaud[31a] and Junès[85a] have reinvestigated the gross intrahepatic distribution of portal vein, the hepatic artery and the hepatic vein. They also co-ordinated the topography of these vessels with the course of the intrahepatic bile ducts and established a

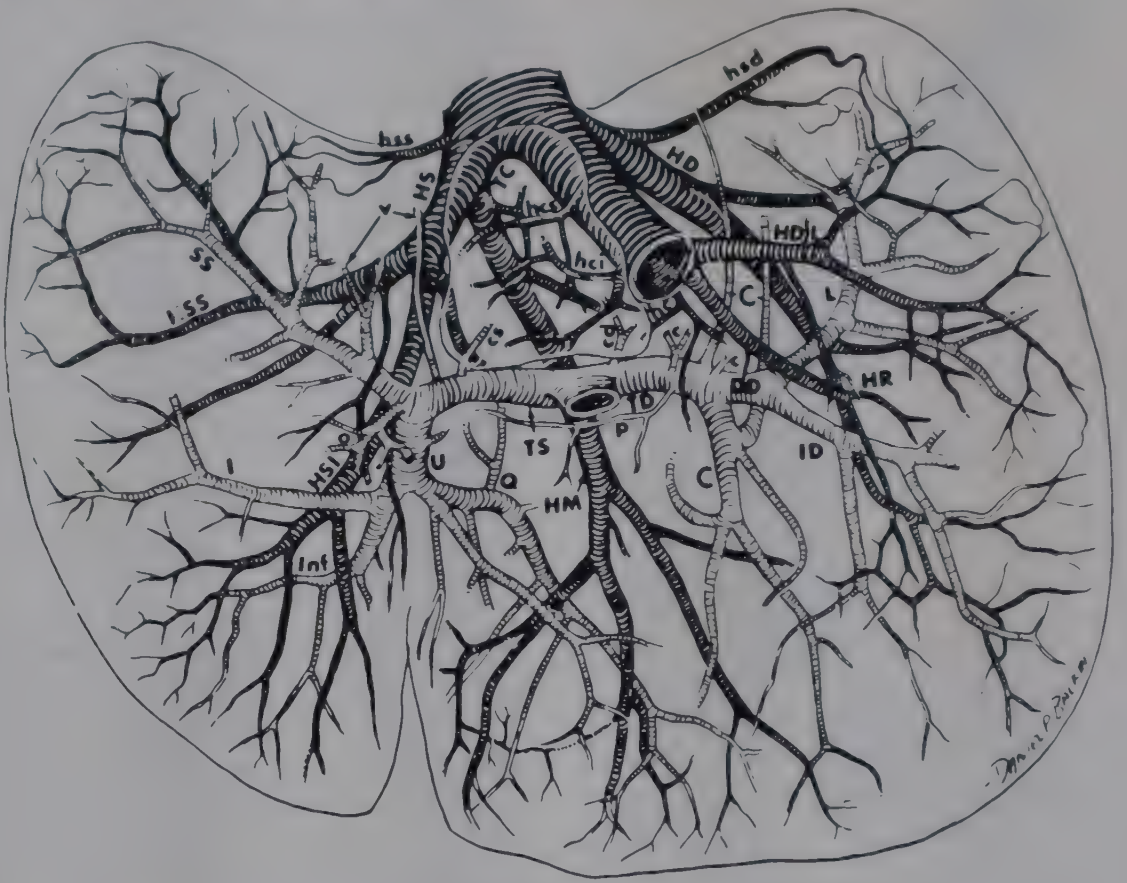


FIG. 14. Corrosion preparation of the liver of a 5-year-old child.
Portal venous system: light. Hepatic veins: dark.
c, ramulus processi caudati. C, rami centrales lobi dextri.
es, ramulus caudatus sinister. ed, ramulus caudatus dexter.
DD, pars distalis trunci dextri. DV, ductus venosus. hc, venula hepatica processi caudati. hci, venula hepatica caudata caudalis aut inferior. hcs, venula hepatica caudata cranialis aut superior.
hsd, venula hepatica cranialis aut superior dextra.
hss, venula hepatica cranialis aut superior sinistra.
HDL, vena hepatica dorso-lateralis dextra. HD, vena hepatica dextra.
HCD, vena hepatica dorso-caudalis. HM, vena hepatica media (HMV, its ventral portion, HMD, its dorsal portion in the fetus).
HR, vena hepatica dorsalis. HS, vena hepatica sinistra.
HSI, radix caudalis aut inferior venae hepaticae sinistrae.
HSS, radix cranialis aut superior venae hepaticae sinistrae.
I, ramus intermedius. ID, ramus caudalis aut inferior dexter.
Inf, ramus caudalis aut inferior lobi sinistri.
IS, truncus communis ramorum intermedii et caudalis aut inferioris lobi sinistri.
L, ramus lateralis dexter. o, ramulus omentalis. p, ramulus paracysticus.
pu, venae paraumbilicales. Q, rami quadrati.
SS, ramus cranialis aut superior lobi sinistri.
TC, truncus communis venarum hepaticarum sinistrae mediaeque.
TD, pars transversa trunci dextri. TS, pars transversa trunci sinistri.
U, pars umbilicalis trunci sinistri. v, ramulus venosus.
VCC, vena cava caudalis aut inferior. VPC, vena portae communis.
VU, vena umbilicalis.
(Elias, H., and Petty, D.: Am. J. Anat. 90:59-112)

new nomenclature for these structures. We shall follow their description (Fig. 14).

Portal Vein. The portal vein divides in the portal fissure into the left and the right hepatic trunci, which form an angle of 90° with each other. The left truncus is longer than the right and consists of transverse and umbilical parts. The latter is the remainder of the umbilical vein. It has a longitudinal course and continues into the round hepatic ligament. Thus a bend is formed between transverse and umbilical parts of the left trunk. The para-umbilical veins, important hepatofugal collaterals within the falciform ligament (p. 27), spring from the umbilical part of the left portal branch.

LEFT PORTAL BRANCH. This branch ("truncus") divides into 3 major branches (rami). The *"ramus superior or dorsolateralis"* (Hjortsjö)[77, 78] has a straight course and supplies the dorsolateral parts of the left lobe. The *"ramus intermedius"* supplies the middle part (about one fourth to one half) of the left lobe. The *"ramus inferior"* irrigates the caudal part of the left lobe. There are also some smaller branches supplying areas in the paracystic region and the quadrate and the caudate lobes.

RIGHT PORTAL BRANCH. This branch ("truncus") is from 2 to 3 cm. long and supplies that part of the right lobe lying to the right of the mid-line of the caudate lobe and to the right of the gallbladder. Besides smaller branches to the tuber omentale and the caudate lobe, the right trunk gives off major branches ("rami") to the 3 major territories situated to the right of the above-mentioned line. Each territory is supplied by a major ramus or by a group of rami. Their point of origin from the right truncus and their course vary greatly.

The "rami centrales" supply the area close to the plane separating the territories of the right and the left portal trunci.

The right lateral "ramus" feeds blood to an area of hepatic parenchyma extending from the highest point of the right lobe to its middle or even its caudal margin.

The right inferior "ramus" supplies a triangular area near its caudolateral angle. The major intrahepatic branches have, in spite of their individual variations in course, a definite spatial arrangement. Each territory depends on its major vessel for blood supply. There is little anastomosis between the macroscopic branches, but large intercommunication at the level of the sinusoids.

Hepatic Artery. Segall[155] likened the straight intrahepatic arterial branches in the younger individual to those of a maple tree and the tortuous branches of the older ones (over 40 years) to those of a bare apple tree. He also described numerous intercommunications between right and left hepatic trunks situated in the capsular folds of the portal fissure. Ligation of one hepatic arterial trunk still permitted him to inject the entire liver through the other truncus.

The intrahepatic arterial branches follow the smaller portal branches quite closely, "climbing along them like a vine on a tree." This feature can be observed also at the microscopic level.[92] There is an absolute irregularity in the branching of the arterial trunks and the major rami. They do not parallel the corresponding portal channels or the major intrahepatic bile ducts. Co-ordination of the courses of the branches of portal vein, hepatic artery and bile duct is accomplished in the peripheral parts of the liver, at the level where tridimensional branching is the major law for the housing of a maximum of parenchyma in a limited space. Also, the dome-shaped diaphragm may help to bring about the hemispheric hepatic surfaces underneath which tridimensional growth is favored by ideal conditions.

Hepatic Veins. The hepatic veins empty into the inferior vena cava where it lies in the groove of the posterior surface of the liver. They are enveloped by the coronary ligament. Since catheterization of the hepatic veins for the determination of hepatic blood flow has become a current procedure,[17, 160] and guided catheterization of the hepatic veins has permitted their roentgenography,[147] a brief outline of the intrahepatic branches of these veins may be useful.

An upper group of 3 major hepatic veins (right, middle and left) empty into the inferior vena cava.

LEFT HEPATIC VEIN. This vessel drains the left liver lobe. It is composed of 2 major radicles: an upper one coming from the upper half and a lower from the lower half of the territory that they drain.

Middle Hepatic Vein. This vein carries blood from the central parts of the liver, i.e., from areas irrigated by the right and the left portal trunci. The middle vein sometimes unites with the left hepatic vein to form a short common trunk before emptying into the vena cava.

Right Hepatic Vein. This vessel is the remainder of the cardiac portion of the right omphalomesenteric vein. It drains the territory to the right of the Sérégé gallbladder-caval line (p. 2).

Several smaller and inconstant veins empty below the group of the major 3 (2) veins into the vena cava. They drain blood from around the gallbladder, from the caudate process and from areas below the dorsal and the dorsolateral surfaces of the right liver lobe.

The intrahepatic course of the valveless hepatic veins is straight and simple. Their smaller branches are in direct contact with the hepatic parenchyma. There are frequent anastomoses among the various branches of the hepatic veins.

There is a definite spatial relationship between the branches of the hepatic veins and those of the portal vein and the hepatic artery. The branches of the hepatic vein interdigitate with the afferent vessels. This architectural arrangement is maintained up to their finest ramifications. A uniform and quick drainage from all parts of the liver is accomplished thereby. The regular interdigitation of the radicles of the hepatic veins (the central veins) with the tridimensionally arranged, terminal, afferent channels brings about a hexagonal pattern in the hepatic parenchyma at the microscopic level. The distance between two such central veins is equal to the width of one hepatic acinus.

This distance is halved by the perpendicularly running pair of afferent axial vessels of the acinus (Fig. 4). Now the veins are found to be situated at the periphery of the structure that they drain, an arrangement that corresponds to the rule in vascular anatomy.

C HEPATIC COLLATERAL CIRCULATION

Arterial Channels. The frequent fatal outcome after severance of the hepatic artery in humans and in laboratory animals has led for a long time to the belief that the hepatic artery is a terminal vessel. A review of this problem[123] has shown that Haberer[64] in 1904 was the first to prove experimentally that ligation of the hepatic artery proximal to its gastroduodenal branch is not fatal. However, the study of the collateral hepatic circulation did not advance until it was demonstrated that in the dog all branches of the hepatic artery can be ligated with impunity when the animal is treated with antibiotics postoperatively.[124] The liver deprived of the hepatic arterial channels develops a rich collateral arterial supply on which it survives.[56, 63, 62] The literature on this subject has grown at a rapid pace since ligation of the hepatic artery was carried out in human patients for the treatment of the sequelae of portal hypertension.[152, 13]

The hepatic artery is provided with collateral flow through its anastomoses with adjacent arteries arising from the celiac axis and the superior mesenteric artery. Good collateral circulation becomes manifest in cases of gradual occlusion of the artery. The liver as an outgrowth of the gut shares one of its architectural features, the vascular arcade. The supramesocolic organs are provided with blood by their own vessels and by collaterals that run in modified arcades. In fact, collateral circulation is due to the persistence of modified pathways of fetal circulation. At the fetal period of our life the organs lie closer together, and their vascular interrelationship is more intimate. Growth increasing the distance between the organs weakens their vascular interconnections. Thus the gastro-epiploic, the pancreaticoduodenal and the primary branches of the colic arteries represent the *dorsal* anastomosis of the embryonic ventral splanchnic arteries, while the left and the right gastric and hepatic arteries are the equivalent of the *ventral* anastomosis of the fetal ventral splanchnic arteries. The many aberrant hepatic arteries described in about 50 per cent of human cases and their anastomosis with the regular vessels are similarly modified vascular arcades. The frequent and extensive communication between the ultimate and the penultimate terminals of the right, the middle and the left hepatic arteries[127] that takes place in the capsular folds within the fossa for the umbilical vein and in the region around the caudate lobe[58] denotes the same arching principle that the splanchnic vessels follow before sending their terminals into the organ. Of course, there are weak points in these anastomosing arcades, and the liver is placed in a "bad corner." Sudden interruption of the hepatic arterial supply through the celiac axis always means putting all hope on collaterals, if any.[13, 58]

The main collaterals of the common hepatic artery are: right and left gastrics, right and left gastro-epiploics, gastroduodenal, supraduodenal, retroduodenal, superior and inferior pancreaticoduodenals, aberrant hepatic arteries and inferior phrenic arteries.

In the liver of the rat and the dog, after interruption of the arterial supply revascularization is provided also by the increasing pericholedochal arterial network.[36, 151] We wonder how much the rich ramifications of the supraduodenal and the inferior pancreaticoduodenal arteries present around the supraduodenal and the retroduodenal parts of the common bile duct are capable of a similar task in humans. The role of the hepatic arterial collaterals in the relief of experimentally induced hepatic coma was stressed recently by Rappaport and associates.[151a]

Portal Channels. L. Pick[140] has divided the portal collaterals into *hepatopetal* and *hepatofugal*. The hepatopetal pathways develop in cases with unimpeded intrahepatic circulation but with extrahepatic blockage of the portal vein. The blood bypasses this obstruction by using normal and anomalous channels which enlarge and accommodate the increased flow through them.

The number and the size of the hepatopetal collaterals depend on the site of portal obstruction. They usually consist of: (1) deep cystic veins; (2) epiploic veins of the lesser omentum and the hepatocolic and the hepatorenal ligaments; (3) veins in the wall of the common bile duct; (4) diaphragmatic veins; (5) veins of the suspensory ligament of the liver; (6) the para-umbilical veins.

In dogs in which an Eck fistula had been formed by the classical technic, we found that hepatopetal collaterals developed in spite of a portacaval anastomosis, permitting free flow of portal blood into the inferior vena cava. It is difficult to explain why the portal blood continued to flow through the narrow intrahepatic pathways.

The hepatofugal collaterals shunt the blood from the abdominal viscera around the intrahepatic obstacle. McIndoe[113] classified these collaterals on an embryologic basis in 3 groups:

1. *Veins located in the gastro-intestinal tract at the junction of absorbing epithelium with protective epithelium.* In portal hypertension, varices are formed in the "stomacho-esophageal and hemorrhoidal plexuses."[172] The former shunts blood from the left gastric (coronary) vein via the inferior hemiazygos and through the diaphragmatic and the azygos veins into the superior vena cava. The hemorrhoidal plexus transfers blood from the superior rectal (inf. mesent.) vein via the middle and the inferior rectal veins into the inferior vena cava. Both plexuses are vulnerable and give rise to prolonged bleeding in patients suffering from portal hypertension.

2. *Veins occurring at the site of the obliterated fetal circulation, the so-called accessory portal system of Sappey.* These are the para-umbilical veins in the falciform and the round ligaments. They unite with the epigastric and the internal mammary veins as well as with the azygos vein through the diaphragmatic veins. Veins may pass along the round ligament to the umbilicus and there develop prominent varicosities known as the "caput medusae." A large vein over which a loud murmur can be heard is seen there in cases with Cruveilhier-Baumgarten syndrome. Its superficial tortuous course was displayed by phlebography.[161] Other varieties of collaterals can be observed in the many ramifications of the venous channels in the thoracicoabdominal wall.

3. *Veins in the abdomen found at all sites where the gastro-intestinal tract and the glands derived from it become retroperitoneal in their development or adhere to the abdominal wall because of pathologic processes.* These veins of Retzius can arise from the duodenum, the omentum, the spleen, the pancreas, the small intestine and the colon. They establish connections between the portal bed and the ascending lumbar azygos and renal veins. The "portorenal plexus," consisting of anastomoses between the left renal vein and the portal beds in the pan-

creas, the spleen and the descending colon,[172] is of clinical importance. Had its function been understood earlier, the possibility of alleviating portal hypertension by splenorenal anastomosis[105] might have been recognized sooner. Simonds[162] gives a classical description of such a naturally occurring anastomosis which was disturbed during splenectomy with fatal consequences. Other rare portacaval shunts pass via the adrenal vein.[54]

Within the hepatic parenchyma collateral channels are formed by anastomoses between smaller branches of the portal and the hepatic veins, the tributaries of the caval system. Moschcowitz[130] made an extensive study of their genesis and considered them as intrahepatic Eck fistulae. Recently, their presence was demonstrated by multicolored injection of cirrhotic liver specimens.[143]

Summary: The collateral circulation of the liver, as of other organs, reminds us that we should not think of our vasculature as an unchangeable system of canals. In spite of its definite morphology, the vascular system is subjected during life to many changes to which, fortunately, it is able to adapt itself.

D. PATHWAYS OF HEPATIC CIRCULATION

The circulation of the liver is characterized by its dual blood supply. As in the similarly supplied lungs, vital metabolic changes of the blood are effected in the liver. From these organs the blood is sent almost directly to the heart for distribution. However, the dynamics in the pulmonary and in the portal circuits differ markedly. Whereas, the venous pulmonary stream is driven through its capillary bed by the muscle of the right ventricle, and the pulsatile flow is conditioned by the respiratory phases, the flow in the portal vein could be compared with that of a swampy river. Having its sources in the capillary network of the large splanchnic marsh, the movement of the blood is slow and is subjected to many fluctuations. The velocity and the pressure of the portal stream are very much determined by the flow through the hepatic delta which, in turn, changes with the phases of respiration. If one observes the exposed portal vein of a dog, one is amazed by the gain in speed of the portal blood stream; the latter becomes turbulent during inspiration. Indeed, the hepatic veins within the parenchyma do not collapse during inspiration, and the aspirating force of the thorax has its full effect on the entire sinusoidal network. The vascular branches of the portal and the hepatic veins interdigitate and run close to each other. They are separated by only small parenchymal masses, the length of a sinusoid or half the width of an acinus, that is, the distance between its axial vessels and central vein. After the ingestion of food, the muddy bed of the intestinal capillaries is flooded, and the tide in the portal stream rises. During exercise, however, the circulation in the musculocutaneous areas is increased at the expense of that in the splanchnic area, and the hepatic minute volume drops. Thus, inflow into the splanchnic area and outflow from the hepatic sinusoidal network determine the volume of flow and the pressure level in the portal vein. Other factors influencing inflow and outflow are the number and the width of collateral venou channels, and the amount of arterial bloo flowing through the liver.

There is a vicarious relationship betwee arterial and portal blood passing through th liver. The controlled competition of inflo takes place where the hepatic artery meet the portal vein. This junction is arteriola capillary or sinusoidal. Thus, as in othe vascular areas, the regulation takes place a the terminal vascular branches which, in th liver, we defined as the afferent axial chan nels of the acinar structural and function units. The blood coming up in an intermi tent flow through the portal branch and i pulsating jets through the companion arteri twig disperses like a fountain. It runs throug the sinusoids down into the radicles of th hepatic veins and waters and nourishes th parenchyma of liver acini. The various wa of branching and anastomosing of the te minal afferent vessels with vascular are situated above and below a hexagonal fie (Fig. 5) indicate that the structural units a intimately connected with each other by the blood vessels and form *one* parenchym mass.

Inflow and outflow from the sinusoi delta are regulated by an intricate slu mechanism, the morphology and the nerv control of which have not yet been inve gated fully. Thanks to this marvelous p of sphincters at the inlet and outlet venules, the arterioles and the capillaries, the arterial and the portal streams, coming into the same compartment under a remarkable pressure difference, further each other's flow instead of inhibiting it. The arterial jets break up the stagnant portal blood in the sinusoids and send it on. The rushing blood column may exert a siphoning effect on communicating lateral sinusoids and empty them. Empty sinusoids opening up offer no resistance to the inflow of low-pressured portal blood. The opening and the closing of adjacent blood channels by sphincters has a valvular effect similar to that in the heart cavities, where low-pressured blood is passed to a chamber that is later under higher pressure in its active phase.

Under still unknown conditions, the portal stream, which keeps the sinusoidal system filled (sometimes one third of the entire blood volume is stored in it) may detour its blood from the large peripheral zone of the sinusoidal delta and short-circuit it by direct channels into the large hepatic veins. Also, extrahepatic collateral venous channels are used to transfer the blood quickly into the inferior vena cava.[34] Thus the portal circulation time is reduced, and the blood returns more quickly to the heart.

The collateral arterial circulation also plays a definite role in the liver. This becomes manifest under pathologic and experimental conditions. After stepwise ligation of all branches of the hepatic artery and the portal vein in a dog, the liver, this huge vascular organ, can survive on collateral circulation alone.[151]

From the related data, much of which has been gathered since the observation of the intrahepatic circulation in vivo,[92, 170, 156] one might be inclined to believe that we already know a great deal about the hepatic circuit interposed between the splanchnic capillaries and the heart. However, most of the data concern only the changing circulatory phenomena. We lack knowledge of the underlying causes. Further investigation of the morphology and the physiology of the sphincter mechanisms that distribute and regulate the blood supply of the hepatic parenchyma and integration of their function into the regulatory mechanisms of the splanchnic area will advance the physiology, the pathology and the therapy of the liver.

THE LYMPH VESSELS OF THE LIVER

In the human liver there is a well-developed subserous hepatic network that communicates with the lymph vessels of the gallbladder (p. 33). The deep lymphatic channels run in the portal tracts where they are visible as the spaces of Mall,[120] especially when serous exudation is present.[75] The lymphatics surround the branches of the hepatic artery and the portal vein up to their finest ramifications. The lymph from these vessels is drained toward the lymph nodes of the hilum of the liver. Frequently, the lymphatics surrounding the tributaries of the hepatic veins are overlooked. They are along the walls of the tributaries of the hepatic veins and drain into the nodes around the inferior vena cava.

Experimental production of ascites by constriction of the inferior vena cava above the hepatic veins[115] blocks the efferent lymph vessels in the wall of the great vein. This blockage brings again to our attention the possible role of the hepatic lymph vessels in the formation of ascites.

The lymphatic drainage within the hepatic parenchyma and its reticulum is still under discussion. Although some believe that from one third to one half of the body lymph originates in the liver, lymph capillaries have not yet been detected between the parenchymal cells. Disse[38] in 1890 put forward the theory of lymph spaces existing between the longitudinal fibers that surround the hepatic sinusoids. The walls of these clefts consist of a structureless fine ground substance and fine fibrils forming a membrane. These findings have been supported by some,[95, 50, 45] while others deny the existence of a perisinusoidal lymph space.[120, 99, 104, 168] Trowell (1946) also denies the existence of perisinusoidal lymphatics but asserts the presence of a gelatinous protein matrix between the sinusoidal wall and the liver cells. In its fluid phase this matrix becomes the tissue fluid that percolates to the nearest lymphatics around the axial vessels and the portal tracts. This concept is supported by the observation of lymph flow in vivo.[138] Popper[141] considers the perisinusoidal spaces as agonal changes of the tissue. Investigation with the electron microscope shows no space of Disse[38] either in the normal organ or in a liver where serous exudation was produced by allyl formate or histamine.[53]

NERVE SUPPLY OF THE LIVER

Sympathetic fibers deriving from bilateral ganglia T 7 to T 10 and synapsing in the semilunar ganglion of the celiac plexus intermingle with fibers from the right and the left vagus and the right phrenic nerve to form the hepatic nerve plexus.[61] It surrounds the hepatic artery as a thick coat and ramifies around the bile ducts. The innervation of the arteries is exclusively by the sympathetic fibers, while the bile ducts are innervated by both sympathetic and parasympathetic fibers. Some fibers follow the vessels and the bile ducts into their finest ramifications and send off branches supplying the contents of the portal tracts;[102, 2] others pass into the parenchyma and end in small knobs.

THE BILIARY SYSTEM

Ducts

Bile excretion starts in the intercellular bile capillaries and canaliculi which empty into the smallest bile ductules (p. 18). The uniting bile ductules form the terminal "interlobular" ducts. The latter are lined by tall cuboidal epithelium and follow the course of the terminal axial branches of the portal vein surrounding them in a plexiform way. From the confluence of the terminal bile ducts larger ducts arise. Their epithelium is taller and contains mitochondria; their walls are thicker; also, they are surrounded by the larger amount of connective tissue present in the portal tracts. The peribiliary arterial plexus is woven around these ducts and is in intimate connection with the outpocketings of their walls described already by Beale (1856).[11]

Plexus and parietal sacculi help concentrate the bile by the absorption of water.[74] Considering the weight of the liver and the volume of hepatic blood flow (1,500 cc./min.), a larger bile secretion than the daily outflow from the bile duct might be expected. An absorptive mechanism in the smaller bile ducts similar to that in the renal tubules is suggested.[148] The observations with the electron microscope of fine papillae protruding into the lumen of the bile capillaries[136] (Fig. 2) and of the striated border of the isoprismatic epithelium lining the bile ductules[18] may corroborate this suggestion.

Intrahepatic Ducts. The wall of the microscopic intrahepatic bile ducts is formed by dense fibrous tissue which contains many elastic fibers. The mucosa formed by tall to columnar epithelium tends to be folded. The localized occurrence of smooth muscle fibers in the wall of the ducts near the hilum of the liver forms the morphologic basis for the narrowing of the bile ducts seen in the cholangiograms.[164] Recently, topographic studies of the intrahepatic distribution of the bile ducts have been carried out to enable a correct interpretation of the cholangiograms.[77, 78, 48, 164] Exact knowledge of the interhepatic topography of the major bile channels is required when anastomosis between them and the intestinal lumen must be established in order to bypass a heavily scarred bile duct.

In the hilar region there is no co-ordination between the major ducts and the major branches of the portal vein. In the peripheral parts of the liver branches of portal vein, hepatic artery and bile ducts run together. Of all the major intrahepatic bile ducts the most constant in its course is the *ductus cranialis aut superior lobi sinistri*. It runs straight toward the suspensory ligament and is found when the liver is approached from its upper left corner.[48] On the right side the *ramus caudalis aut inferior dexter* is easily accessible.[48]

Extrahepatic Ducts

COMMON HEPATIC DUCT. This duct arises from the confluence of the right and the left intrahepatic trunks, which leave the liver in the right end of the portal fissure to become the right and the left hepatic ducts. The common hepatic duct is 3 cm. long and is situated to the right of the hepatic artery and in front of the portal vein. It is joined by the cystic duct at its right side and in an acute angle to form the bile duct (ductus choledochus). This manner of junction is considered as normal. Anatomic variations in the types of anastomosis between the cystic and the hepatic ducts are of surgical importance (Fig. 15).

BILE DUCT (DUCTUS CHOLEDOCHUS) The length of the bile duct depends on the site of junction of the cystic duct with the common hepatic duct. If this junction is very low, the choledochus is short (Fig. 13). Its average length is quoted as 7 cm.; its diameter, as of the size of a goose quill. The free or supraduodenal part of the choledochus runs downward and slightly to the left and lies in the right border of the lesser omentum, anterior to the aditus to the lesser sac. Usually, surgical revision of the common bile duct is carried out at this free part; also, it is the most common site of strictures.

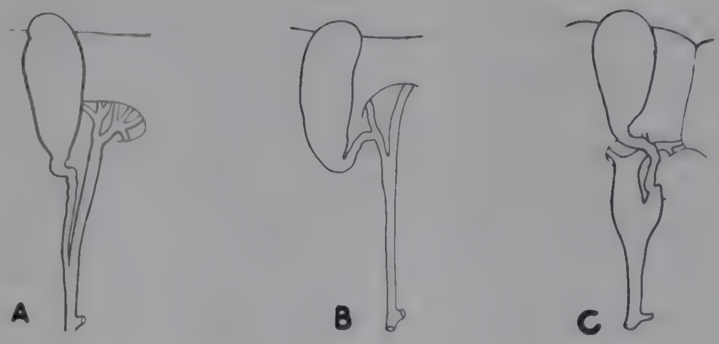
The pancreatic part of the bile duct passes retroperitoneally behind the first portion of the duodenum. It then runs in a groove on the posterior surface of the head of the pancreas, where it is situated in front of the inferior vena cava. At the left side of the duodenum it is joined in 89 per cent of cases by the pancreatic duct (Wirsung) and forms the ampulla of Vater (3 to 5 mm. long).

The duodenal or intramural part of the choledochus has been the object of many studies aiming to clarify the intricate sphincter mechanism present here.[134, 122, 22, 84, 15, 16, 167] It is destined to regulate a one-way flow of biliary and pancreatic secretion into the intestine. In their passage through the duodenal wall the united bile and pancreatic ducts form a wartlike elevation of the mucosa called the papilla of Vater. A shallow dilatation inside the papilla, in average 3 mm. deep and as some believe (Job[84]) quite inconstant, is called the ampulla of Vater. Cholangiography reveals in about one fourth of the cases a reflux from the bile duct into the pancreatic duct. In these cases the openings of both ducts lead into a common cavity. Then biliary disease can easily reflect upon the pancreas.

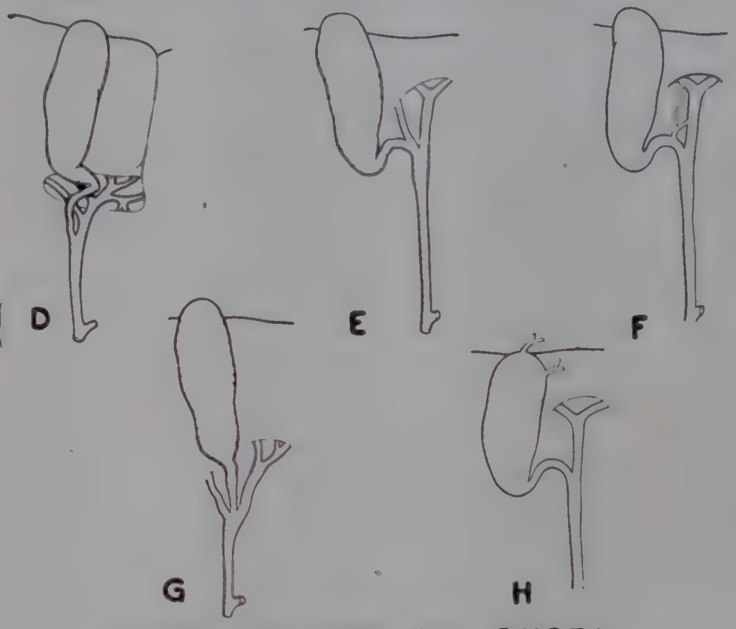
Sphincter of Oddi. The circular smooth muscle fibers surrounding these structures are defined as the sphincter of Oddi. It is composed of:

1. *The Choledochus Sphincter.* It consists of circular muscle fibers that surround the intramural portion of the common bile duct in its course through the intestinal submucosa. This sphincter, which is always present, constricts the lumen of the bile duct.

2. *The Pancreatic Sphincter.* It is present only in a small number of individuals (33%) and does not represent a real muscle ring.[94]



VARIATIONS IN THE CYSTIC DUCT



ACCESSORY HEPATIC DUCTS

FIG. 15. Anomalies of cystic and bile ducts. A, B, C are variations in the length and the course of the cystic duct: (A) low junction of cystic duct with bile duct; (B) high junction of cystic duct with bile duct; (C) swerving course of cystic duct before joining the common bile duct. D, E, F, G, H are accessory right hepatic ducts. (Of 95 gallbladders and bile passages injected in situ with melted wax and then dissected, 6 had accessory hepatic ducts in positions of surgical danger. Of these, 3 joined the common hepatic duct near the cystic duct [D], 2 joined the cystic duct [E], and 1 bile duct [G] and also the gallbladder [H]. All except H were sketched from specimens.) (Grant, J. C. B.: Method of Anatomy, ed. 5, Baltimore, Williams & Wilkins)

Thus the reflux of bile from the bile duct into the lumen of the pancreatic duct is possible.

3. *The Sphincter Ampullae*. It consists of longitudinal fibers surrounding a weak layer of sparse circular fibers.[90] The longitudinal fibers in contracting shorten the ampulla and raise mucosal folds to prevent reflux of intestinal content into the lumina of the ducts.

GALLBLADDER

The gallbladder is a receptacle for bile (30 to 50 ml.). In the form of a pear-shaped sac 3 cm. wide and 7 cm. long, it lies on the undersurface of the right liver lobe. Its parts are designated as fundus, corpus and neck. The fundus projects beyond the inferior border of the liver at the site where the lateral margin of the rectus crosses the costal margin. The body is directed upward and to the left. Posteriorly, fundus and body are in close relation with transverse colon and duodenum, respectively. Gallstone perforations into these viscera are possible. Where the neck of the gallbladder is attached to the liver by areolar tissue, it is reached by the cystic artery. The neck is curved anteriorly in an S-shaped way and when enlarged forms the so-called Hartmann's pouch. The mucous membrane of the neck forms a spiral valve of Heister which continues into the cystic duct. The latter arises from the left upper corner of the pouch and has a proximal valvular and a distal smooth portion. The spiral valve has the function of regulating bile flow both ways—into and out of the gallbladder. During the fasting state the gallbladder receives bile from the hepatic duct through the cystic duct. When stimulated by food or cholecystokinin the gallbladder delivers the concentrated bile through the cystic duct into the common bile duct and the intestine.[82, 83] Some consider the mucosal folds of Heister's valve as an architectural device to prevent distension and collapse of the cystic duct when sudden change of pressure occurs in the gallbladder or the common duct.[103]

Histology of Extrahepatic Ducts and Gallbladder. *The cystic, the hepatic and the common bile ducts* all possess a mucosa, a submucosa and a muscularis. The mucosa consists of a single layer of columnar epithelium and a tunica propria which contains mucous glands. These are of the type of utricular glands, and their openings are visible to the naked eye. They are lined by simple cylindrical epithelium and are surrounded by a wall of connective tissue very rich in capillary network. Some believe that they represent small receptacles in which the bile is concentrated as in the gallbladder. In the dog these *sacculi* dilate and increase in number after cholecystectomy.[166]

The wall of the extrahepatic ducts is formed by a strong layer of connective tissue fibers into which sparse muscle elements are interspersed, except for the region of the neck of the gallbladder and at the lower end of the common duct where muscle rings are conspicuous.[72] Taking into consideration the absorptive and the sphincter mechanisms it is to be emphasized that the extrahepatic bile ducts are not passive conducting tubes of bile. They take part in the concentration and the intermittent discharge of bile.

The gallbladder is lined by a mucosa thrown into multiple folds beautifully described by William Boyd.[14] They serve to increase the absorptive capacity of the organ. The epithelial lining of the mucosa is columnar, the cells being provided with a striated border (for absorption). Glands of the tubulo-alveolar type are found in the region of the neck. They are the only glands to produce mucus in the gallbladder. The Rokitanski-Aschoff sinuses are only outpouchings of the mucosa into defects of the muscularis favoring bacterial retention and inflammation. However, the ducts of Luschka are lined with mucosa of the bile duct type.[111] They are situated in the areolar tissues of the hepatic surface of the gallbladder and communicate with intrahepatic bile ducts rather than with the gallbladder cavity. Their presence is an indication for drainage of the gallbladder bed following cholecystectomy A small amount of areolar tissue separate the mucosa from a skimpy layer of decus sated smooth muscle bands well develope only in the fundus and the neck of the organ Their arrangement is similar to that of th urinary bladder.[6] There are many elasti fibers in the body of the gallbladder. Th serosa is attached to the muscularis by subserous layer of connective tissue th contains the vessels, the nerves and th lymphatics.

Blood Supply of Bile Ducts and Gallbla

der. The arterial supply of the bile ducts comes mainly from the right hepatic artery. Branches of the posterior, the superior and the postero-inferior pancreaticoduodenal arteries forming abundant anastomotic loops contribute also to the formation of Zuckerkandel's plexus around the common bile duct.[41]

A continuation of this plexus within the liver along the intrahepatic bile ducts forms the peribiliary plexus. In the dog whose hepatic artery has been ligated these vascular networks become pathways by which the hepatic parenchyma connects with collateral arterial vessels mainly from the phrenico-abdominal and inferior pancreaticoduodenal arteries. The periductal plexus in such animals has been demonstrated by catheterization and roentgenography of the celiac axis in vivo.[147a, 151]

The cystic artery usually arises from the right hepatic arterial branch, joins the gallbladder at its neck, divides into 2 branches that run under the serosa of the gallbladder, supplying this organ as a terminal artery. Injury to this vessel or its parent artery is followed by gangrene of the gallbladder. In some cases, where the gallbladder is buried more deeply into the liver substance, collateral blood supply from the hepatic parenchyma may prevent this cataclysm. The anomalies of its arterial supply have been described by Flint[55] and Browne,[21] and recently investigated by Michels.[127] The veins of the gallbladder empty into the portal vein or form a vein at the neck of the gallbladder which passes directly into the hepatic parenchyma joining the sinusoids.

Lymph Vessels of Bile Ducts and Gallbladder. The lymph vessels of the hepatic, the cystic and the upper parts of the common bile duct empty into glands of the hilum. Those of the lower part of the common bile duct drain into glands around the head of the pancreas.

The lymph vessels of the gallbladder already investigated by Sudler (1901) are connected intimately with the lymph vessels of Glisson's capsule.[165] The importance of this connection for the "liver-gallbladder" syndrome was stressed recently.[52] The gallbladder, although an outgrowth of the intestine, has no lymph follicles. However, there is a superficial subserous network of lymphatics and a submucous one which does not penetrate the mucosal folds. They empty into the "lymph gland of the neck" of the gallbladder.

Nerves. The nerve fibers supplying the extrahepatic ducts derive mainly from the sympathetic hepatic plexus laced around the hepatic artery. These also receive filaments from the right and the left vagus nerves. Some nerve fibers deriving from the plexus can be seen running along the common bile duct. Sparse ganglion cells are present in the muscularis and the mucosa of the gallbladder. Most of the nerve cells are found in the fibromuscular layer of the cystic duct.[112] Nervous connection with the spinal system is brought about by fibers from the right phrenic and the musculophrenic nerves. As these nerves derive from the third or the fourth cervical nerve, the anatomic basis for shoulder pain in gallbladder disease is seen readily.

Anatomic Variations of Bile Ducts and Gallbladder. These anomalies are much less frequent than those in the vascular supply of the liver and its bile receptacle. The absence or the obliteration of the bile duct is noticed early in the newborn. It is fatal when not corrected in time. Absence of the gallbladder is normal for the rat, the horse and the deer. It is rare in humans (1 in 4,000 cases) where in two thirds of the cases it will show some symptoms.[39] Usually it is associated with absence of the cystic duct.

Accessory hepatic ducts, low junction of the branches of the hepatic duct, anomalies in the anastomoses between cystic duct and hepatic duct, and congenital cystic dilatation of the common bile duct are the most common malformations of the duct system[118, 154] (Fig. 15).

The common hepatic duct can receive accessory hepatic ducts or it may be completely absent. In the latter case 2 hepatic ducts run separately and join close to the duodenum. Then the right duct will anastomose with the cystic duct[30] (Fig. 15).

Double gallbladder usually produces symptoms of biliary disease and sometimes can be discovered by cholecystogram or during operation.[129] This anomaly is due to nonconfluent cavitation of the solid gallbladder anlage. Bilobed, hourglass-constricted gallbladders, those with folded fundus (phrygian cap) or persistent septum favor retention and inflammation. The gallbladder can be completely buried in liver substance or attached loosely to it by a mesenterium (floating gallbladder). The latter variety is preferred by the surgeon.

TOPOGRAPHY

Liver

The liver occupies the right hypochondrium and the epigastric space. It extends into the left hypochondrium and into the right lumbar region. Protected in its greater part by the ribs, only a small part of its anterior surface touches the anterior abdominal wall. The organ fits perfectly into the dome of the diaphragm and is held there like a ball in a socket by the intra-abdominal pressure. Interposed between diaphragm above and transverse mesocolon and colon below, the liver divides the subdiaphragmatic compartment into a suprahepatic and a subhepatic space.

Suprahepatic Space. The *left* suprahepatic space is separated from the *right* by the falciform ligament. The latter has an anterior division extending between anterior surface of liver, diaphragm and anterior abdominal wall. The posterior *right suprahepatic division* is delimited by the convex hepatic surface, the diaphragm and the coronary ligament. Eighty per cent of all infections are found in this latter division.[173]

Subhepatic Space. The subhepatic space extends between the concave surface of the liver and the transverse mesocolon, the colon, the duodenum, the stomach and the anterior abdominal wall. The *right subhepatic area* has an anterior and a posterior division. The latter extends between the inferior surface of the liver, the posterior peritoneal reflection of the coronary ligament and the upper pole of the right kidney. Frequently, the anterior subhepatic division is entered by the surgeon to labor in the operating fields of gallbladder and common bile duct. The *left subhepatic area* is divided by the frontally orientated stomach and the lesser omentum into an anterior and a posterior compartment (lesser sac). All these spaces and their divisions when infected can be entered by surgical procedures that follow the extrapleural and extraperitoneal routes in order to avoid the spread of infection in the thoracic and the abdominal cavities.

Gallbladder and Bile Ducts

The topography of gallbladder and bile ducts is discussed under "Biliary System," and the variations of the hepatic vessels under "The Vessels of the Liver." The abnormal topography of the hepatic pedicle results from the frequent anomalies encountered in these structures. Normally, vessels and bile duct are disposed in 2 layers within the hepatoduodenal ligament. The ventral layer contains the bile duct and the hepatic artery, while the portal vein lies in a more dorsal plane. A thoraco-abdominal incision approaching this vessel from behind is therefore suitable for carrying out an anastomosis between portal stem and superior vena cava. The hepatic artery, a vessel much attacked by the surgeons lately, lies in the left border of the hepatoduodenal ligament, at the margin where its thin and transparent gastrohepatic neighbor abuts. As a landmark to identify the site where the knot will be slung around the hepatic artery, Madden[119] advises the exposure of the gastroduodenal artery branching off from the hepatic artery and arching over the portal vein. This large vein having the hepatic artery on its medial side and running underneath the gastroduodenal artery allows the operator to know for certain whether the hepatic artery is ligated proximally or distally to the gastroduodenal artery, an important hepatic collateral.[64]

Summary: Although the liver occupies a shielded corner of the abdominal cavity because of its size, topography and vascular connections, it shows intricate relationship with almost all abdominal organs. Therefore, changes in these organs may be reflected first in the liver.

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Chapter 2

PHYSIOLOGY OF THE LIVER

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CONTROL OF CONSTITUENTS OF THE BLOOD

The function of the liver is essentially that of regulation of the concentration of the individual constituents of the blood. There are present in normal or abnormal blood few substances which the liver does not specifically add to the blood or remove from the blood. In addition, the liver alters, for synthesis or for destruction at some stage or other, almost every chemical constituent of the blood. Conversely, every tissue of the body is in part dependent on the liver for its nutrient supply from the blood and the removal of a variety of noxious agents. Any diffusible substance injected into the blood is removed rapidly by the liver—so rapidly that in less than 5 minutes the level of the substance injected into the blood is reduced to less than half the value found in the blood of a completely dehepatized animal after a similar injection.

The intimate relationship between the blood and the liver is also indicated by the fact that approximately one third of the cardiac output of blood passes through the liver. The liver capillaries in intimate contact with the hepatic cells are found to contain from 15 to 20 ml. of blood for each 100 Gm. of liver. Similar determinations of capillary blood content of muscle and intestine indicate only 0.5 and 2 to 3 ml. of capillary blood for each 100 Gm. of tissue, respectively. Most of our knowledge of the functions of the liver is dependent on this intimate relationship of the blood and the liver as indicated by clinical and experimental studies. These have included the change that occurs in the blood, the urine and the tissues of patients having demonstrable liver disease and of animals after experimental alteration of the liver by surgical or chemical means. These studies have also involved analysis of constituents of the blood entering the liver compared with similar analysis of the blood flowing from the liver.

EFFECTS OF HEPATECTOMY

Clinical Course. The basis of many of our ideas of liver function has been the observation of the changes shown to occur in animals after complete removal of the liver. In such preparations substances formed only by the liver do not appear in the blood or tissues, and those destroyed by the liver increase in amount unless tissues other than the liver are also active in such destruction. All other tissues of the body continue to function apparently in a normal manner for many hours after the liver has been removed completely, except for the alterations in the constituents of the blood specifically increased or decreased by the absence of the liver.[6] If hepatectomy is performed successfully, the animal recovers from the anesthetic and from the immediate effects quickly. The subsequent clinical course is definite and varies but slightly in different animals. Observers of the hepatectomized animal at this time pronounce it normal; it walks around, responds to call and exhibits the usual interest in its surroundings. Within 3 to 8 hours in the untreated animal definite and characteristic symptoms begin to appear. The first symptom noticed is muscular weakness coincident with a decrease and subsequent loss of reflexes. After a variable period, usually not more than 1 hour, there is a sudden return and exaggeration of the reflexes; muscular twitchings and then general convulsions occur, in one of which the animal dies.

Hypoglycemia. The symptoms and the

death of the untreated hepatectomized animal always are due to hypoglycemia. If glucose is administered at any time before death of the animal, recovery from symptoms is prompt, and within a few minutes the animal again appears to be normal. If death from hypoglycemia is prevented by continuous or intermittent administration of glucose, dogs have survived in normal-appearing condition for as long as 56 hours after the liver has been removed. Finally, however, characteristic symptoms develop, and death occurs irrespective of the level of the blood sugar. The animal becomes restless and usually vomits. Respiration becomes rapid and labored. The animal becomes ataxic and apparently loses both the senses of sight and hearing, because objects are not avoided in walking, and no response to sound is elicited. The animal becomes somewhat spastic, and coma develops which may persist for several hours. When death occurs it is usually sudden and quiet. These symptoms and death occur more rapidly after blood loss or the administration of substances other than glucose and sufficient fluids to maintain the fluid balance of the animal. Even the continued administration of glucose in excess, so that abnormally high values for blood sugar are obtained, appears to hasten the time of onset of these symptoms.

Toxicity. As might be anticipated, the levels of many chemical constituents of the blood and the tissues become progressively abnormal following complete removal of the liver. However, it should be noted that no substance has been found to accumulate in quantities sufficient to account for death due to the absence of the liver, nor has any lethal deficiency been demonstrated except for that of glucose as has been mentioned previously. After hepatectomy animals appear to be much more susceptible to many toxic substances than are normal animals of the same species. In many instances this reflects the ability of the liver to abstract substances from the blood and may or may not depend on any specific detoxicating power of the liver. With certain substances the liver is the only organ of the body capable of making the chemical transformation of detoxication.

AMMONIA is converted to urea only by the liver,[7] and the rapid conversion of ammonia to urea by the normal animal permits the administration of many times the amount of ammonia that would be fatal to the liverless animal.[19] The symptoms of *ammonia poisoning* are similar in the intact animal and in the liverless animal and occur in both when the concentration of ammonia in the blood is elevated to the same level. Ammonia, mostly of intestinal origin, does accumulate in the blood in the absence of the liver but in amounts which are tolerated by both intact and liverless animals, and they may be maintained for hours without producing any recognizable symptoms.

AMINO ACIDS. Amounts of several amino acids which when injected are tolerated by intact animals are toxic in the absence of the liver. However, the toxic symptoms appear to depend on the concentration of the amino acids in the blood, which is greater when the liver does not remove them from the blood than when it does remove them. Most of the metabolic deaminization of amino acids occurs in the liver with urea formation and conversion of the deaminated acid to glucose. In the absence of the liver these processes do not occur; amino acids accumulate[8] in the blood and the tissues, and larger amounts are excreted in the urine. The increased free amino acid content of brain tissue and cerebrospinal fluid is especially interesting where the normally occurring free amino acids may be 3 or 4 times their normal concentration.[15] Glutamine, which is normally in greater concentration than any amino acid, is increased most, and the increases in the amino acids appear to be approximately in proportion to the usual distribution found. No specific amino acid has been found to be increased outstandingly. The terminal coma and death of the hepatectomized animal are not related directly to the amount of amino acid accumulated in the brain.

In animals receiving excessive amounts of glucose postoperatively terminal symptoms of liver removal develop when the elevation of the free amino acid content of the cerebrospinal fluid and the brain is less than half that found in dehepatized animals not so treated but which have shown similar symptoms. Administration of insulin stimulates protein formation in both normal and dehepatized animals and will minimize the increase of amino acids of the blood and tissues of the liverless animal.[14] However, the increased amino acid content of the brain and the cerebrospinal fluid is not influenced by insulin.[1] This may indicate only the lack of effect of insulin on the brain, but the continued increase of amino acids of the brain does indicate some liver-brain relationship. Brain protein hydrolysis with liberation of amino acids may be accelerated in the absence of the liver, or the absence of some hormone from the liver fails to promote protein synthesis in the brain similar to the protein-forming stimulus provided by insulin to other tissues.

ALKALOIDS, STRYCHNINE AND NICOTINE are more effective in the liverless animal than in the intact animal, and the liver appears to have some specialized ability in their destruction.[23] However, chemical conjugation of many toxic substances is as rapid in the blood of liverless animals as in intact animals. The liver does not appear to be the sole site of destruction or conjugation of the following substances: phenol, guiacol, camphor, benzoic acid, salicylates, epinephrine, ephedrine and guanidine.

Bilirubin: Accumulation in the Blood and Excretion in the Urine. Bilirubin is formed in the tissues of the reticuloendothelial system, largely in the bone marrow and the spleen. Removal of the liver does not reduce greatly the amount of bilirubin formed. The absence of the liver prevents excretion of bilirubin into the gastro-intestinal tract, and jaundice appears, owing to the accumulation of bilirubin in the blood and the tissues.[20] The bilirubin in the blood of the liverless animal reacts slowly ("indirect") with the van den Bergh reagent. Bilirubin is excreted in the urine of the liverless animal and gives the prompt ("direct") van den Bergh reaction.[4] In humans in whom the blood bilirubin reacts "indirect," as in hemolytic icterus, no bile pigment is excreted in the urine. Since the bilirubin of the bile and the bilirubin of the blood of obstructive jaundice (resorption icterus) react "direct" with the van den Bergh reagent, the conversion of bilirubin formed extrahepatically to the "direct"-reacting bilirubin of the bile is accomplished by the liver. This "direct" bilirubin is excreted as such in the urine if biliary excretion is impaired by obstruction of the biliary ducts or injury to the liver.

Cole and Lathe and Cole, Lathe and Billing adapted reverse phase column chromatography to the separation of the pigments of jaundiced serum. They have isolated 3 different bilirubins from human serum. Spectrographic analysis of these pigments showed them to be different compounds, 2 of which reacted "direct" with the van den Bergh reagent and 1 of which reacted "indirect." The process of separation frees these compounds from proteins and other possible combinations. Cole and Lathe have established the fact that bilirubins react differently with the van den Bergh reagent because of different molecular structure.

With the methods of Cole and Lathe my colleagues and I found that after complete removal of the liver in the dog and the rat 2 bilirubins accumulate in the blood. One reacts "indirect" with the van den Bergh reagent and appears to be identical with the pigment found in normal serum which is increased in hemolytic icterus. This pigment is not excreted in the urine. The other pigment reacts much more rapidly with the van den Bergh reagent but definitely more slowly than the direct reaction typical of obstructive jaundice. This pigment is like the "indirect" pigment in its solubility in chloroform but chromatographic separation shows it to be much less polar and more like the "direct"-reacting pigment in this respect. This pigment likewise is not excreted as such in the urine. The amount of this pigment accumulating in the blood after hepatectomy is several times as much as that of the "indirect"-reacting pigment. Also, fairly large amounts of this pigment are converted by the kidneys to the typical "direct"-reacting bilirubin which appears in the urine. So far, this pigment has not been identified in the blood of humans with various types of icterus.

Apparently, 2 bilirubins are formed from hemoglobin outside of the liver. One is the "indirect"-reacting bilirubin, similar to that of normal human blood and increased in hemolytic icterus, which is not excreted in the urine and is changed only slowly by the liver and excreted in the bile. Most of the extrahepatic bilirubin formed is different from the "indirect"-reacting pigment and is converted rapidly by the liver to the "direct"-reacting pigment which is excreted in the bile or accumulates in the blood in resorption icterus.

In the examination of animals dying with extensive hepatic injury, regardless of the methods by which the injury was produced, one does not find the typical symptoms or chemical changes that are found following complete removal of the liver.[6] The animal usually succumbs before the entire function of the liver is lost. Many of the functions of the liver are performed efficiently by the remaining portion of the liver, even though a large portion of the liver is damaged or destroyed. The detoxicating functions of the liver seem to be altered most, and the symptoms seem to relate more to the intoxication produced than to the total amount of functioning hepatic tissue remaining. Some of the toxic substances may be derived also from the metabolism of material liberated by autolytic disintegration of injured hepatic tissue. These considerations are especially notable in regard to animals with hepatic lesions which may not appear to be very detrimental under ordinary conditions and may be associated with only minor changes of sulfobromophthalein retention. Such animals may fail rapidly following a surgical procedure which would be of little consequence to normal animals. Following operation, these animals are markedly lacking in resistance, and acute degenerative changes may occur rapidly in the injured liver. Preoperative preparation with diets rich in carbohydrates and administration of glucose following operation have enabled animals to recover under circumstances that usually have been fatal to similar animals without administration of carbohydrate.[3]

CHANGES IN SIZE AND COMPOSITION OF THE LIVER

There are considerable cyclic changes in the size and the composition of the liver at various times of the day.[16] The major changes are brought about by the assimilation of food and subsequent alterations in the character of the metabolic activity dependent on the amount and the nature of the absorbed and stored foodstuffs. For example, following the ingestion of sugar, glycogen is added to the liver, utilization of carbohydrate increases, and there is an associated decrease in utilization of protein and fat. When the influx of sugar ceases, the glycogen of the liver is utilized because of the increased carbohydrate metabolism. With the relative depletion of available carbohydrate which ensues, protein metabolism is increased again, and glucose formation from protein replaces again the glycogen in the liver. In animals fed only a single meal a day the changes in the size and the composition of the liver are considerable. Most of the increase in liver weight after feeding is attributable to additions of water which parallel the increase and the subsequent decrease in glycogen and a similar, though less marked change in protein content of the liver. Changes in the fat content of the liver under these circumstances are not marked. Some drugs appear to have effects in relation to meals which indicate a greater susceptibility during the period when the glycogen content of the liver is low than when it is high.

The chemical composition of the liver may be altered greatly by hepatic disease, hepatotoxic agents or dietary deficiencies alone, or by combinations of these 3 factors. With such gross changes in the liver its functions of regulation of concentration of substances in the blood are altered surprisingly little. As much as half of the liver may be fat, that is, more than 10 times the normal fat content, with no reflection in the lipoids of the blood. Conversely, lipemia seldom increases the fat content of the liver. Accumulation of fat in the liver occurs only following toxic injury to the hepatic cells or in association with nutritional deficiencies which create conditions similar to those of toxic injury.[3] Fasting alone may produce a fatty liver during the first few days of fasting. Increased amounts of fat may be demonstrated a few hours after toxic injury to the liver. Removal of the cause of hepatic injury, elimination of the toxic substance, or replacement of the dietary deficiency allows the fat content of the liver to return to normal in a few days.[5] Other constituents of the liver change with varying fat content: the water content is proportionately less; the protein content is somewhat less; and the glycogen content is usually less. However, the administration of carbohydrates under these conditions usually will increase the glycogen content of the fatty liver only somewhat less than it does in a normal liver. Continuous excessive infusions of glucose may increase the glycogen content to as much as 20 per cent of the liver.[10] If this occurs, excretion of bile pigment and sulfobromophthalein is impaired.

REGENERATIVE POWER AND PROCESSES

In addition to the physiologic reserve possessed by the liver, there is also present marked regenerative power,[13] which enables the remaining hepatic cells to multiply so that the mass of active hepatic tissue is restored again after removal of, or extensive injury to, large parts of the liver. The idea of regeneration of the liver comes down from antiquity, first revealing itself in the myth concerning Prometheus, whose liver was gnawed daily by the tormenting vulture at the behest of Jove. In animals from which single or multiple lobes of the liver may be removed surgically, the remaining portion of the liver enlarges in a few days. The lobules do not hypertrophy but undergo a hyperplastic, budding process at their periphery, productive of new lobules so that in a few weeks sections reveal tissue almost indistinguishable from normal liver.

The liver appears to possess an infinite capacity for regeneration. By serial operations every 10 weeks my colleagues and I have removed in total more hepatic tissue than was present at the first operation. At the termination of the experiment the remaining lobe of the liver was enlarged to slightly more than the original weight of the whole liver. During this process no signs of hepatic deficiency were observed except for the transient upsets immediately following operations, which probably were due to injury of the remaining hepatic tissue rather than to actual deficiency because of the removal of tissue.

Similar regenerative processes are involved in the repair of the liver following injuries produced by the hepatotoxic agents of liver disease except that the repair takes place adjacent to and intermingled with the degenerating tissue. Certainly by the time the stage of nodular cirrhosis is reached all of the liver cells have been replaced several times. Regeneration of the liver has been shown to be greatly diminished in the presence of obstructive jaundice or hepatic toxic agents, and after extensive cirrhotic processes are present. The marked reduction of the blood flow to the liver as accomplished by portacaval anastomosis greatly reduces the regenerative ability of the liver.[17] For this reason the continued administration of hepatotoxic agents is much more deleterious to the Eck fistula animal than to the intact animal.

Revascularization of the liver occurs rapidly concurrently with regeneration so that after regeneration is complete the same amount of portal blood flows through the same number of hepatic lobules all supplied with normal portal, arterial and hepatovenous radicles. If the portal blood is diverted from the liver at the time of partial hepatectomy, regeneration does not occur, and the hepatic lobules continue to function with their arterial blood supply, but this does not increase appreciably. However, when cirrhotic changes are present in the liver considerable diversion of portal blood from the liver has occurred already, and there has been an increase in the volume of arterial blood flowing to the liver. Under these circumstances regenerated lobules of the liver often are found to be supplied largely by arterial blood.[22] Ligation of most of the major branches of the hepatic artery acutely interferes with both the arterial and the portal blood flow through the part of the liver involved. Within a day or two anastomotic channels have developed so that again the liver is well supplied with arterial blood. If the anastomosing arteries also are occluded, necrosis of the parts of the liver deprived of arterial blood occurs. After extensive ligation of the branches of the hepatic artery in dogs, life may be maintained for several days by the administration of antibiotics. Material injected into the aorta at this time is found in arterioles adjacent to every part of the liver that is not necrotic.[18] Hepatic tissue does not survive without arterial blood, and arterial revascularization in the liver is accomplished rapidly.

FACTORS IN THE FUNCTIONAL CAPACITY OF THE LIVER

The functional capacity of the liver depends on the efficiency of the hepatic cells, the blood supply to the liver and the amount of materials supplied by the blood for transformation by the liver. The total flow of blood from the liver is the average of the flow from the numerous sinusoids, which vary considerably from time to time in their individual rates of flow. Some blood may be shunted rapidly through some sinusoids or through nonsinusoidal tissue of the liver and be exposed little or not at all to hepatic cellular influence. The flow of blood to the liver depends on arterial pressure and on the flow from the portal area. Both of these sources of blood are relatively independent of the liver itself, except for the processes of hepatic disease which increase the resistance to flow from the sinusoids and cause the diversion of portal flow into collateral channels. The blood flow to the liver is uniformly constant under basal resting conditions but is increased greatly by exercise, excitement, taking of food, or other conditions which increase the cardiac output of blood.[2]

Removal of Sulfobromophthalein from the Blood. The rate of removal of sulfobromophthalein from the blood is an index of the functional capacity of the liver which reflects both the blood flow to the liver and the capacity of the hepatic cells. If sulfobromphthalein is injected intravenously at a constant rate, the liver removes it from the blood at the same rate unless the capacity of the liver is exceeded.[9] The concentration of sulfobromophthalein in the blood of the hepatic vein is less than that of the blood going to the liver (arterial blood and venous blood from other organs show no difference). The amount of sulfobromophthalein given each minute divided by the difference in milligrams per milliliter between the content of sulfobromophthalein in arterial blood and that of hepatovenous blood indicates the volume of blood passing through the liver each minute. The calculated blood flow through the liver of a cirrhotic animal is near normal but is increased or decreased according to the relative size of the liver. The total amount of sulfobromophthalein removed is reduced markedly because a smaller proportion of the sulfobromophthalein is removed from the blood as it passes through the liver of the cirrhotic animal. In the Eck fistula animal the total removal of sulfobromophthalein is also less, but the proportion of sulfobromophthalein removed from the smaller amount of blood passing through the liver is greater than that of normal animals. In the same way it has been found that the removal of injected ammonia[21] from the smaller amount of hepatic blood is proportionately greater than in the normal animal. Similar results have been found with the hepatic removal of glucose after its injection.

Release of Glycogen into Blood. When the blood glucose is not elevated, the blood from the hepatic vein always contains more glucose than is present in arterial blood. Calculations indicate that regardless of amount or condition of the liver, or marked changes in the flow of blood through the liver, the same amount of glucose is added to the blood by the liver each minute. The increase of concentration of glucose in the blood of the hepatic vein is inversely proportional to the volume of blood flow through the liver in all the conditions of experimental hepatic alterations thus far studied. After injection of insulin there is an increased peripheral utilization of glucose, producing hypoglycemia which in turn is followed by a marked increase in the glucose added to the blood by the liver. This formation of glucose from liver glycogen does not occur if the pancreas is absent but will occur if glucagon is injected. The amount of sugar released by the liver is dependent largely on the amount of glycogen present in the liver at the time of hypoglycemia. Under conditions of small blood flow through the liver the concentration of glucose in the hepatic vein is increased correspondingly. In most conditions of acute or chronic liver injury the glycogen content of the liver usually is reduced, and for this reason the hypoglycemic action of insulin appears to be increased.

Addition or Removal of Metabolic Substances. In addition to the elaboration and the secretion of bile, the liver functions in adding or removing metabolic substances from the blood. For all of these functions it is dependent on the number and the capacity of hepatic cells and their adequate supply of blood. In all animals about 10 per cent of the normal number of liver cells are adequate for the metabolic needs of the body. The liver is able to regenerate new hepatic cells after injury and thus may replace itself many times. The amount of blood, both arterial and portal, flowing through the liver varies greatly with the cardiac output under various physiologic and pathologic conditions. The total hepatic functions are not altered greatly by these variations in blood flow. Signs and symptoms of liver disease appear only after most of the liver is incapacitated. The ability of the liver to repair itself is great, and if further injury can be prevented and the cause of the injury removed, normal function will be restored.

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Chapter 3

BIOCHEMICAL CONSIDERATIONS OF THE LIVER

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INTRODUCTION

The human body is a highly integrated organism whose optimum maintenance or even survival depends upon the functioning of many different organs, tissues and cells. Many of these organs must be capable of variation in function and of compensation for physiologic and disease changes. Therefore, it is somewhat unrealistic to isolate an organ and speak of its biochemistry if the entire organism is being studied. In a discussion of the biochemistry of the liver in the intact mammal many organ interrelations with the liver are known or inferred. For example, the term "hepatic coma" means an abnormal brain response associated with liver failure; the disease state hepatolenticular degeneration connotes a brain and liver interrelationship; while the hepatorenal syndrome suggests a relation with the kidneys. It is the ultimate desire of the clinician, the physiologist and the biochemist to understand the biochemistry of the liver in this sense. Unfortunately, wide gaps in our knowledge exist in the understanding of liver biochemistry in the intact animal.

This does not mean that no knowledge exists. Recent in vitro and in vivo studies have revealed so much information about the chemistry of the liver that no modern authoritative monograph or review combines all this knowledge. Furthermore, considerable data exist on biochemical mechanisms in other tissues, micro-organisms and plants which would seem to hold for liver tissue. There is uncertainty only because original studies on bacteria or other organisms have not been repeated in liver tissue. Many studies done in liver tissue have not been repeated in diseased liver tissue or most unfortunately in intact animals with diseased livers.

Many of the chemical reactions that appear likely to occur from blackboard discussions and from thermodynamic considerations have been shown to occur in the liver. The development and the use of new technics such as chromatography, countercurrent distribution, tracer studies and phys-

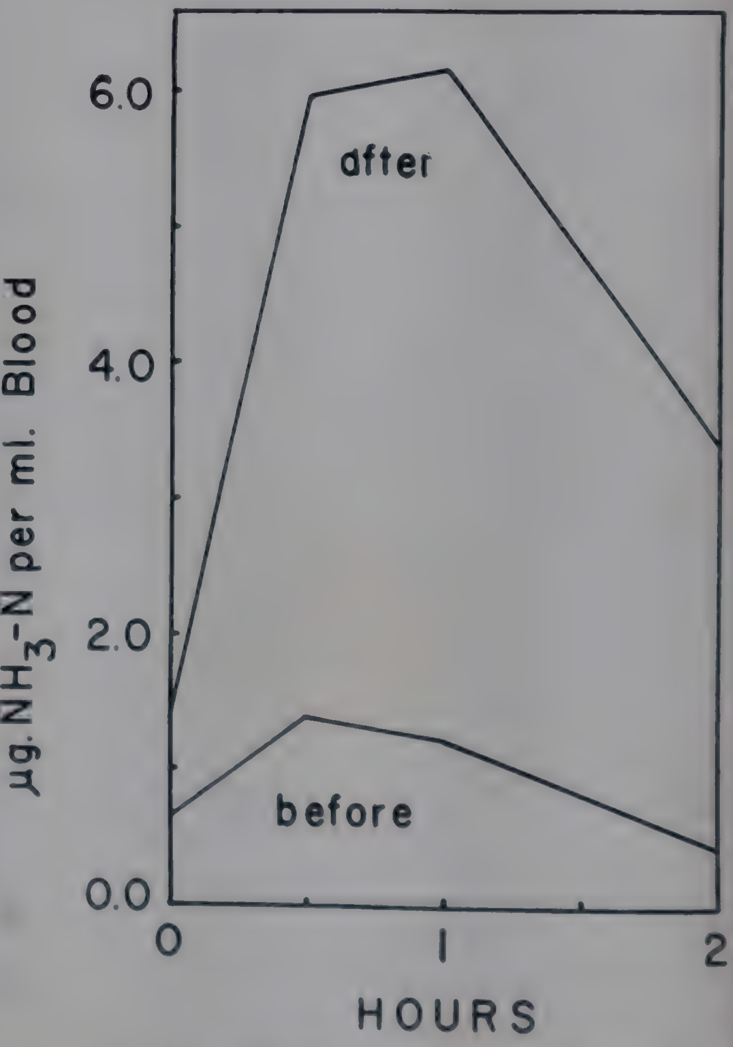

FIG. 16. Ammonium citrate tolerance test in a patient before and after a portacaval shunt.

iologic studies have been yielding important data to fill the gaps in the field of liver biochemistry.

The liver is in the main a chemical mill, in which compounds are burned, altered, broken down, synthesized or excreted. In addition, it plays the role of modifier to many systems. For example, if too much pressor amine is circulating the liver will oxidize it. It continually reduces the level of free circulating endocrines, particularly the steroids. It also provides compounds to be used for further synthesis by other tissues, for example, creatine for muscle creatine-phosphate. The liver is interposed as an important barrier between the portal blood, with its many harmful substances, and the other organs. For example, the rapid intravenous injection of ammonium salts will lead to a high level of blood ammonia, convulsions and death before the liver can remove the ammonia from the peripheral circulation. However, when ingested the ammonia enters the portal blood which flows through the liver directly, allowing removal and preventing the ammonia from entering peripheral blood in large amounts. When blood is shunted around the liver, as is the case in a portacaval anastomosis, ingested substances enter the blood and bypass the liver. Figure 16 shows the oral ammonium citrate tolerance of a patient before and after a portacaval shunt and demonstrates the effect of shunting blood around the liver.

Whether or not the qualitative nature of the reaction of ammonia in the liver is altered by the change of flow through it, the quantitative aspect is certainly different. Observations on patients with shunts who imbibe indicate higher blood alcohol levels and more rapid intoxication. Other effects due to abnormal blood flow or unusual metabolic activity of other organs which affect the liver will be mentioned.

In this discussion of the biochemistry of the liver, the liver function tests are omitted because they are being discussed elsewhere in this book. These valuable tests correlate with, rather than measure, liver function. This section is intended to indicate the bio-

TABLE 1. SOME COENZYMES OR PROSTHETIC GROUPS AND RELATED VITAMINS

COENZYME OR PROSTHETIC GROUP	FUNCTION	VITAMIN INVOLVED
Diphosphopyridine nucleotide (DPN)	Hydrogen acceptor in dehydrogenations	Nicotinamide
Triphosphopyridine nucleotide (TPN)	Hydrogen acceptor in dehydrogenations	Nicotinamide
Adenosine triphosphate (ATP)	Transphosphorylations	
Uridine diphosphate glucose (UDG)	Phosphogalactoisomerase	
Pyridoxal phosphate (B_6)	Transamination, amino acid decarboxylation	Pyridoxine
Thiamine pyrophosphate (B_1)	Cocarboxylase, pyruvate and ketoglutarate oxidation	Thiamine
Flavin mononucleotide (FMN,B_2)	Hydrogen acceptor	Riboflavin
Flavin adenine dinucleotide (FAD,B_2)	Hydrogen acceptor	Riboflavin
Coenzyme A (CoA)	Acyl donor or carrier	Pantothenic acid
Iron-protoporphyrins	In catalase, cytochromes, hemoglobin	
6,8-Dithio-n-octanoic acid	Pyruvate and ketoglutarate oxidation	Bacterial growth factor
?	CO_2 fixation	Biotin
?	1-Carbon particle transfer, purine and pyrimidine synthesis	Folic acid
?	Hemopoiesis, 1-carbon particle synthesis and transfer	Cobalamin, (B_{12})
?	Precursor for folic acid	Para-aminobenzoic acid

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chemical processes which occur in the normal liver, and wherever possible the aberrations caused by disease will be included.

THE ROLE OF ENZYMES*

In order to discuss the chemistry of the liver it is desirable to mention or describe some concepts of biochemistry. Many of the chemical reactions occurring in the liver could possibly take place in a test tube; however, the rate of these reactions would be so slow as to be undetectable and of no practical value. To speed up the reactions, catalysts (enzymes) are needed which will allow the chemicals to react more readily. A few reactions which are nonenzymatic may occur, but even these in the main are enzyme controlled. Many of the enzymes when split yield a smaller nonprotein moiety, the coenzyme or prosthetic group, which is essential for the enzyme action. Many of these coenzymes are made from vitamins such as those in Table 1. The presence of vitamins in these compounds and their presence in liver explains some of the nutritional value of liver.

The protein moiety of enzymes has the ability to act as an electron reservoir which can expand or contract, with the coenzyme functioning as the valve or duct through which the electrons flow. In addition the nature of the coenzyme in certain oxidation-reduction reactions determines the ability to give off or accept electrons. It is interesting to note that in starvation or wasting the liver gets smaller because of protein loss and in the process many enzymes are reduced in amount in the liver. It may well be that these stores of proteins are really enzymes or reservoirs for enzymes or enzyme formation, the loss of which is reflected by diminished chemical reactive capacity. The enzymes are amphoteric and in addition their activity depends upon pH. The optimum pH for maximal activity in vitro may vary from pH 5 for acid phosphatase to pH 9 for alkaline phosphatase. In biologic systems, particularly in the liver, their activity is limited to the pH of the liver cells, approximately 7.0. A severe change in body pH presumably could increase or decrease enzyme activity and cause metabolic effects. In addition, some enzymes in acidosis might be activated while others were being inhibited. The in vivo effect of changes in body pH on enzyme action is not known. However, it has been shown that in diabetic acidosis where the blood pH is diminished, insulin sensitivity is decreased, whereas on return to normal pH the insulin sensitivity increases. Enzyme activity is also directly related to temperature. The change of body temperature during a high fever might be sufficient almost to double the activity of some of the enzymes in the liver. This in vivo change during fever has not been evaluated.

The enzymatic activity may be enhanced by assuring the presence of the trace elements (such as iron, copper, magnesium, molybdenum and manganese) and coenzymes needed by the enzyme. The enzymes of the liver in the normal state have this assurance. In certain experimental trace-element deficiencies or vitamin deficiencies these enzymatic activities are decreased. In disease states of man it seems possible but not yet established that these deficiencies cause reduced enzymatic activities of the liver. Other activators are known, e.g., sulfhydryl compounds such as glutathione for intracellular proteinases. On the other hand, enzyme action may be inhibited by changing pH away from optimum or by reducing temperature. A molecule similar in structure to a substrate but different in some detail may attach to an enzyme more tightly than the normal substrate and prevent its being acted upon. This process of competitive inhibition is well exemplified by malonic acid COOH-CH_2-COOH, which resembles succinic acid COOH-CH_2-CH_2-COOH and prevents succinic dehydrogenase from catalyzing the conversion of succinate to fumarate. The possibility that competitive inhibition plays a role in liver disease exists but has not been demonstrated clearly. When ethionine, an analog of methionine, is fed to rats it can destroy their livers in less than a day. The process is related to competitive inhibition in that ethionine is utilized instead of methionine, whereupon the synthetic process stops. A second type of inhibition is that of enzyme poisons such as Hg^{++}, Ag^{+} or Pb^{++}, arsenic or cyanide, which can tie up free sulfhydryl groups of an enzyme or combine with its coenzyme in a manner to prevent electron changes, which then prevents the enzyme action. Most enzymes have a high degree of specificity in that they catalyze reactions involving a single substrate.

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* Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPN, diphosphopyridine nucleotide, DPN (ox) and DPN (red) represent the oxidized and reduced forms; TPN, triphosphopyridine nucleotide, TPN (ox) and TPN (red) represent the oxidized and reduced forms; FAD, flavin adenine dinucleotide; CoA, coenzyme A; HSCoA, CoA in the sulfhydryl form; UDG, uridine diphosphate glucose; ~, high-energy bond.

Some enzymes, like xanthine oxidase, participate in many in vitro reactions involving several substrates. The actual in vivo specificity within a cell is not known. It appears that the enzymes in cells function as if they were in a production line, offering only selected substrates to certain enzymes in a manner which biologically would increase intracellular enzymatic specificity. The enzyme and the substrate may combine and dissociate, so that an equilibrium exists. Therefore, two intracellular enzymes capable of activating reactions involving a single substrate will compete for the substrate, the tighter enzyme-substrate combination being reflected by the ultimate reaction which occurs. There are numerous possible metabolic pathways that a molecule like pyruvic acid can take, as shown by studies of purified in vitro systems. However, only a fraction of these are quantitatively important in the intact animal. Presumably, the enzyme location (on the production line), the dissociation constant, the availability of reactants such as ammonia, hydrogen, carriers or other factors would determine which pathway is followed. Most of the enzymatic reactions are reversible. For example, glucose-phosphate in the presence of phosphorylase can go to glycogen or vice versa. For the body economy many reactions must go to completion to provide energy continuously. The cellular structure and enzyme organization are such that reversals of many reactions are prevented because the reaction products are passed on to or accepted by other enzyme systems. This phenomenon may be a factor in determining the rate of reactions in vivo or in vitro. For example, in vivo the alcohol dehydrogenase activity has been estimated to be 10 times that of the crystalline enzyme in vitro. In the diseased liver or in the liver of a diseased animal these factors may be playing a role. As mentioned above, the blood supply to the liver determines whether a compound entering the portal blood will go to the liver or to the peripheral blood and other organs before going to the liver. Altering of metabolic pathways in this manner is poorly understood. If the liver and a peripheral tissue can utilize a substrate under normal circumstances, after a meal the liver will get first opportunity to metabolize the substrate. However, if the patient has a portacaval shunt the peripheral tissue will get a greater metabolic opportunity than would normally be the case. The same is true of intravenous therapy. If for some reason it becomes clinically desirable to give the peripheral tissues a greater initial exposure to ingested metabolites in order to favor one metabolic pathway above another, this situation in man could be managed by performing a portacaval shunt to pass portal blood to the periphery. For example, the liver contains the enzyme system for the synthesis of cholesterol from acetate and precursors. If the blood is shunted around the liver so that these substrates for cholesterol synthesis are utilized to a larger extent than normal by peripheral tissues, it might be possible to reduce the rate of cholesterol synthesis. In a selected case of familial hypercholesterolemia where a high incidence of coronary occlusions in young persons occurs a portacaval shunt might be indicated medically. This is only a hypothetical case of how the alteration of blood flow might conceivably be used to alter a metabolic response for clinical advantage. As will be shown later, glucose appears to be metabolized in the liver by the aerobic-shunt mechanism, while fructose is metabolized via the glycolytic scheme. If one of these pathways for carbohydrate metabolism proves to be more desirable in the management of liver disease, the physician may have the opportunity of choosing a metabolic pathway for therapeutic purposes. An understanding of which enzymatic reactions are working best in a diseased liver might provide some help in sustaining a patient.

CELLULAR STRUCTURE AND ENZYME RELATIONSHIPS

As will be shown subsequently, the biochemical reactions occurring in the liver are highly integrated so that complicated reactions occur in steps with the end result being physiologically important. For example, a mole of glucose can be oxidized in the liver to CO_2 and water. If for some reason a breakdown product of glucose such as lactate is infused, the lactate enters the metabolic pool at the proper place and then continues through the oxidative sequence to CO_2 and water. These reactions are catalyzed and controlled by numerous enzymes, some of which can perform more than one function. In addition, under the proper in vitro circumstances, a molecule of pyruvate can go through many different reactions, depending upon which enzymes are present. In the liver, as in other tissues, the major pathways undoubtedly are determined by the location and the orientation of these enzymes in the micro-anatomic structures of the cell. The substrate is activated and reacts in a manner permitted or induced by the environment in the cell, with reactants readily available at the proper time and place. In this way interference and competition among biochemical reactions are avoided.

In order to study the micro-anatomic "geography" the cytochemists have been trying to disrupt cells but not their particulate con-

TABLE 2. LOCALIZATION OF ENZYMES AND RELATED COMPOUNDS IN LIVER CELLS* †

	ENZYME SYSTEM OR COMPOUND	CONCENTRATION (WHOLE TISSUE = 1)
Nuclei	D-Amino acid oxidase	1.0
	Arginase	0.6, 1.1, 2.5
	Adenosinetriphosphatase	0.1, 1.7
	Adenosine-5-phosphatase	0.2, 2.9
	Alkaline phosphatase	0.1, 0.4, 1.9
	Adenosine deaminase	1.8
	Nucleoside phosphorylase	0, 1.0
	Uricase	0.1, 1.0
	DPN Nucleosidase	?
	Synthesis of DPN	5.5, 6.0
	Desoxypentose nucleic acid	7.3-8.1
	Pentosenucleic acid	1.0
Mitochondria	Cytochrome oxidase	3.1
	Cytochrome c	2.3
	DPN-Cytochrome c reductase	1.2
	TPN-Cytochrome c reductase	2.3
	Succinic dehydrogenase	2.4, 2.8
	α-Ketoglutaric oxidase	1.5
	Oxalacetic oxidase	1.8
	Octanoic oxidase	2.3
	Glutamic dehydrogenase	3.3
	β-Hydroxybutyric dehydrogenase	?
	Synthesis of citric acid	?
	Synthesis of ATP (oxidative phosphorylation)	6.7‡
	Adenylate kinase	?
	Adenosinetriphosphatase	2.2, 2.4, 2.5
	Choline oxidase	3.1
	Betaine aldehyde oxidase	?
	D-Amino acid oxidase	?
	Tyramine oxidase	2.2, ?
	α-Glycerophosphate dehydroginase	?
	Catalase	?
	Uricase	2.5, 3.0
	Rhodanese	?, 4.2
	Cathepsin	2.6
	Glutaminase	3.7

stituents. Then the enzyme content of the various structures is determined. Unfortunately, such studies have been limited to normal or neoplastic tissues. Four cell fractions have been obtained and studied: (1) the nucleus, (2) the mitochondria, (3) microsomes or submicroscopic particles and (4) the soluble components.

NUCLEUS

The nucleus accounts for approximately 12 per cent of the liver cell mass. Hogeboom and co-workers[17] have tabulated the nuclear enzymes, regarding as nuclear only those whose concentration exceeds that in whole tissue. This excludes numerous enzymes present in lower concentrations. Table 2 contains the enzyme or compounds possibly located in the nucleus. Well-defined localization of a compound or an enzyme in the nucleus should show a nuclear-tissue ratio of 8. A compound which manifests this ratio is desoxyribose nucleic acid. From this data no such localization of enzymes in the liver cell nucleus is suggested. One exception is the presence of enzymes synthesizing DPN from ATP + nicotinamide mononucleotide which appears to indicate nuclear localization. Since DPN is the electron carrier for a number of oxidative reactions which occur in the cytoplasm, this synthesis might suggest cytoplasmic control by the nucleus. Other studies indicate that ribonucleic acid probably is synthesized in the nucleus, suggesting a close chemical relationship to DPN which is also a ribose dinucleotide. Glycolytic and oxidative enzymes seem to be absent from the nucleus. The so-called ATPase

TABLE 2—*Continued*

	ENZYME SYSTEM OR COMPOUND	CONCENTRATION (WHOLE TISSUE = 1)
Mitochondria	Acid phosphatase	1.3, ?
	Adenosine-5-phosphatase	?, 0.5
	Ribonuclease	2.2
	Desoxyribonuclease	2.7
	Glutamic-phenylpyruvic transaminase	?
	Glutamic-oxalacetic transaminase	2.3
	Synthesis of:	
	p-aminohippuric acid	2.8
	hippuric acid	?
	citrulline	?
	Vitamins:	
	B_6	1.3
	B_{12}	2.2
	Riboflavin (total)	1.8
	FAD	2.3
	Folinic acid	1.8
	Pantothenic acid	?
	CoA	?
	Citric acid	4.4
	Phospholipid	1.5, 1.8
Microsome fraction	Esterase	4.2
	DPN-cytochrome c reductase	2.5
	TPN-cytochrome c reductase	2.0
	Glucose-6-phosphatase	?
	DPN nucleosidase	?
	Uricase	1.2
	Pentose nucleic acid	2.3
	Phospholipid	?

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[*] Question mark (?) suggests a relatively high concentration, but the analytical data do not permit a calculation of the concentration value.

[†] Based on data in Hogeboom, Schneider and Striebich.[17]

[‡] Value open to some question because of difficulties in the enzyme assay.

in liver nuclei may reflect ATP-dependent synthetic reactions. The ATP may come from the mitochondria via the cytoplasm to the nucleus where it may take part in nuclear reactions such as the synthesis of ribose derivatives as mentioned.

MITOCHONDRIAL FRACTION

The mitochondrial fraction is better defined because of the sturdier membrane (as compared with the more fragile nuclear membrane) which retains large and small molecules during the fractionation. The mitochondria represent 25 per cent of the rat liver cell mass. An enzyme ratio of mitochondria to tissue of 4:1 suggests localization of the enzyme in the mitochondria. This can be seen in Table 2. Several oxidative enzymes, such as those of the citric acid cycle and components of the oxidative chain from DPN to cytochrome, are present here. As would be expected from this presence, ATP is synthesized in the mitochondria. This synthesis may be an exclusive function of the mitochondria which has been called "the power plant of the cell." A number of vitamins and coenzymes are found in the mitochondria. When mitochondrial membranes are ruptured, several enzymatic reactions are enhanced, as if the barrier between mitochondrial enzymes and cytoplasmic substrates had been broken. On the other hand, cytochrome oxidase appears to function better with intact mitochondria, as if certain mitochondrial enzymes were on the surface, exposed to cytoplasmic substrates so that the cytochromes and their oxidases would be present to complete the reactions. After disruption of the particles some enzymes remain attached to particulate matter in such a manner that enzymes can be fractionated by varying centrifugation. The different enzymatic properties suggest structural integration in the mitochondria. The morphologic similarities of liver mitochondria to other tissue mitochondria is matched by biochemical similarities.

MICROSOME FRACTION

The microsome fraction or particulate material of the cytoplasm amounts to 20 to 25 per cent of the rat liver cell. It has a high concentration of pentose nucleic acids, phospholipids and other lipids. About 40 per cent of the microsome fraction is fat and that is mainly phospholipids. These particles are tinted red with a protoporphyrin hemochromogen (not the cytochromes). Table 2 shows some of the known enzyme components. These particles have the ability to transfer electrons and protons from the pyridine nucleotides to the cytochromes but do not participate in oxidative reactions as do the mitochondria. The high pentose nucleic acid fraction and localization of tracers such as labeled alanine in the microsomal proteins suggest a relationship to protein synthesis. The rate and the quantity of incorporation are much higher in the microsomes. Addition of substrates whose oxidation by the mitochondria leads to ATP synthesis facilitates the incorporation of the labeled amino acid into microsomal protein. This again suggests biochemical integration among the cellular components in that mitochondrial oxidation leads to synthesis of ATP which diffuses to the microsomes to participate in protein synthesis.

SOLUBLE FRACTION

The soluble fraction represents the "cell sap." It accounts for 40 per cent of the original cellular protein nitrogen. Many proteins and, as would be anticipated, many enzymes are present in this fraction. Anaerobic glycolysis (oxidation of glycogen or glucose to lactic acid) occurs here. At least 50 per cent of all glycolysis can be accounted for in the soluble fraction of rat liver, suggesting that this important function occurs here to a great extent. Other cellular components stimulate reactions of the soluble fraction.

"The cell . . . is a complicated mosaic of structural units that are endowed with specific biochemical properties. Furthermore, although some degree of functional autonomy may be indicated in the case of certain elements, the mitochondria in particular, there is reason to believe that in no single instance is this autonomy complete but rather that the structural units are mutually dependent on one another in their contribution to the metabolism of the cell."[17] It is of considerable importance that students of liver disease some day understand to what extent this integration or mutual dependence is disrupted in liver disease.

CARBOHYDRATE METABOLISM

Chemistry

The important carbohydrates are those which are or yield the 6-carbon sugars, glucose, fructose, galactose and mannose. These compounds are chemically reactive because of their potentially free aldehyde or ketone group, their many alcohol groups and their lability in alkali (enolization). Although the sugars are depicted as 6-carbon, chain compounds, in reality they exist as ring structures represented in the schematic formulas in Figure 17 which reveal the true chemical and spatial structures of glucose.

The close structural relationship of these sugars allows the liver to convert them to glucose or glycogen readily.

The following terms have been used to define glucose metabolism in the liver.

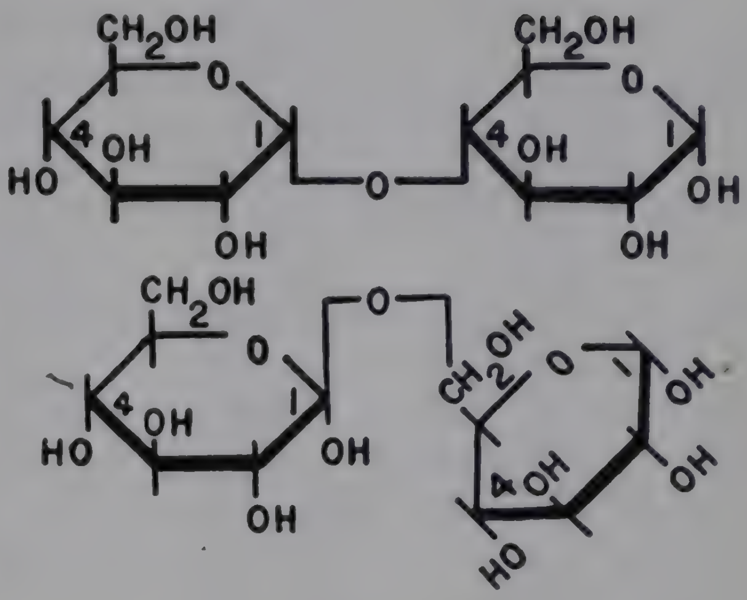


Fig. 17. Two glucose molecules attached in a 1, 4 link as found in the straight chains of glycogen. Two glucose molecules attached in a 1, 6 link as found in the branching points of glycogen.

glucose ——→ glycogen = glycogenesis
amino acids ——→ glucose = gluconeogenesis
glycogen ——→ glucose = glycogenolysis
glucose ——→ pyruvic acid = glycolysis (anaerobic pathway)
glucose ——→ gluconic acid = shunt (aerobic pathway)

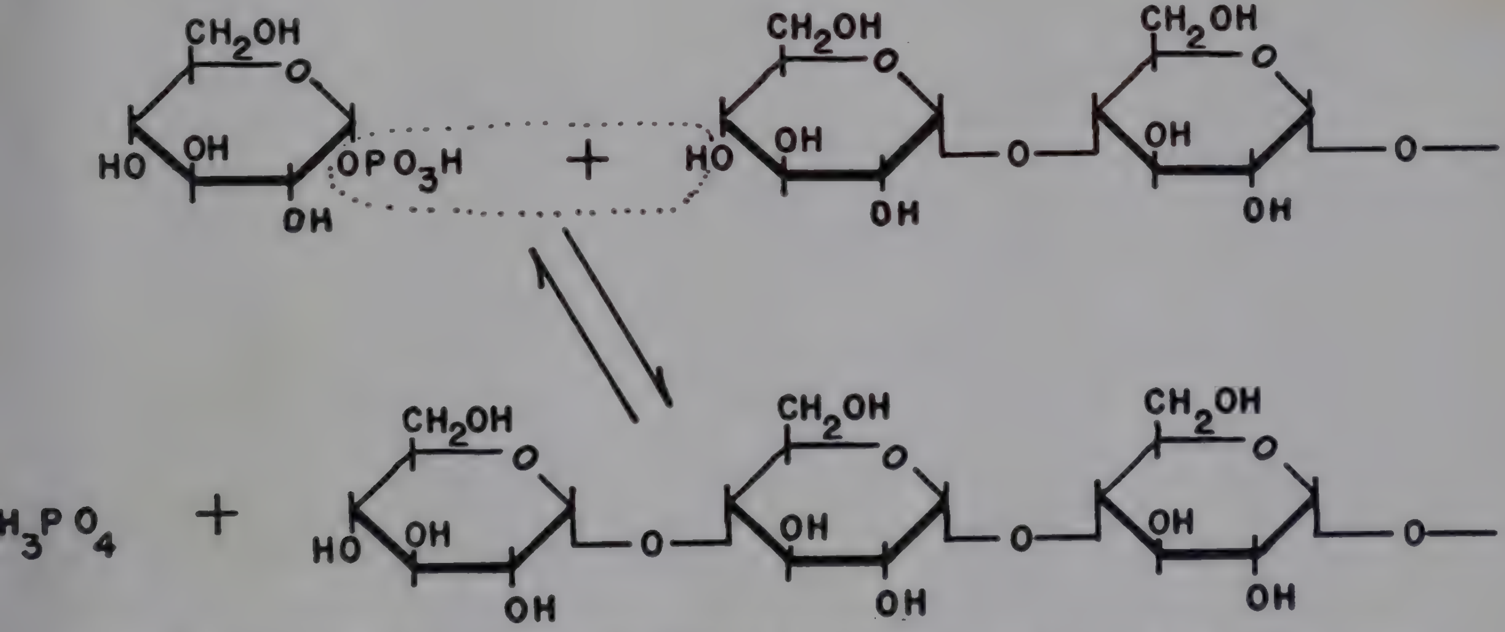


Fig. 18. Addition of glucose-1-phosphate to a glucose chain by splitting off of phosphoric acid. This is the reversal of phosphorolysis. The enzyme involved is phosphorylase.

Glycogen Formation and Breakdown

Glycogen is a glucose polymer which occurs mainly in the liver and in muscle. On acid hydrolysis it yields glucose. Enzymes in liver perform this hydrolysis (glycogenolysis) to provide glucose for the outflowing blood and thereby for the other organs which must have glucose.

The links in glycogen are made by joining 2 glucose molecules at the 1-carbon and the 4-carbon atoms or the 1-carbon and the 6-carbon atoms as shown in Figure 17.

Glycogen synthesis involves 3 enzymatic reactions.[9]

1. Glucose + ATP $\longrightarrow$ glucose-6-phosphate + ADP

This reaction is catalyzed by the enzyme hexokinase or more specifically glucokinase, of which there is an abundance in liver. The structure of ATP is shown in Figure 23.

2. Glucose-6-phosphate $\xrightleftharpoons[\text{glucomutase}]{\text{phospho-}}$ glucose-1-phosphate

In this reaction which is catalyzed by the enzyme phosphoglucomutase glucose-6-phosphate is changed to glucose-1-phosphate.

3. Glucose-1-phosphate $\xrightleftharpoons{\text{phosphorylase}}$ glycogen + inorganic phosphate

This reaction requires the presence of the enzyme phosphorylase, which allows the addition of glucose to chains of glucose. The glucosidic linkages are formed when glucose-1-phosphate reacts with the glucose chains with removal of phosphate as shown in Figure 18.

It should be noted that this reaction is reversible. The splitting of the 1,4-glycosidic link by the addition of phosphate is called phosphorolysis. The enzyme amylase can split certain plant starches by the addition of water or the analogous process of hydrolysis. By phosphorolysis, glucose molecules are re-

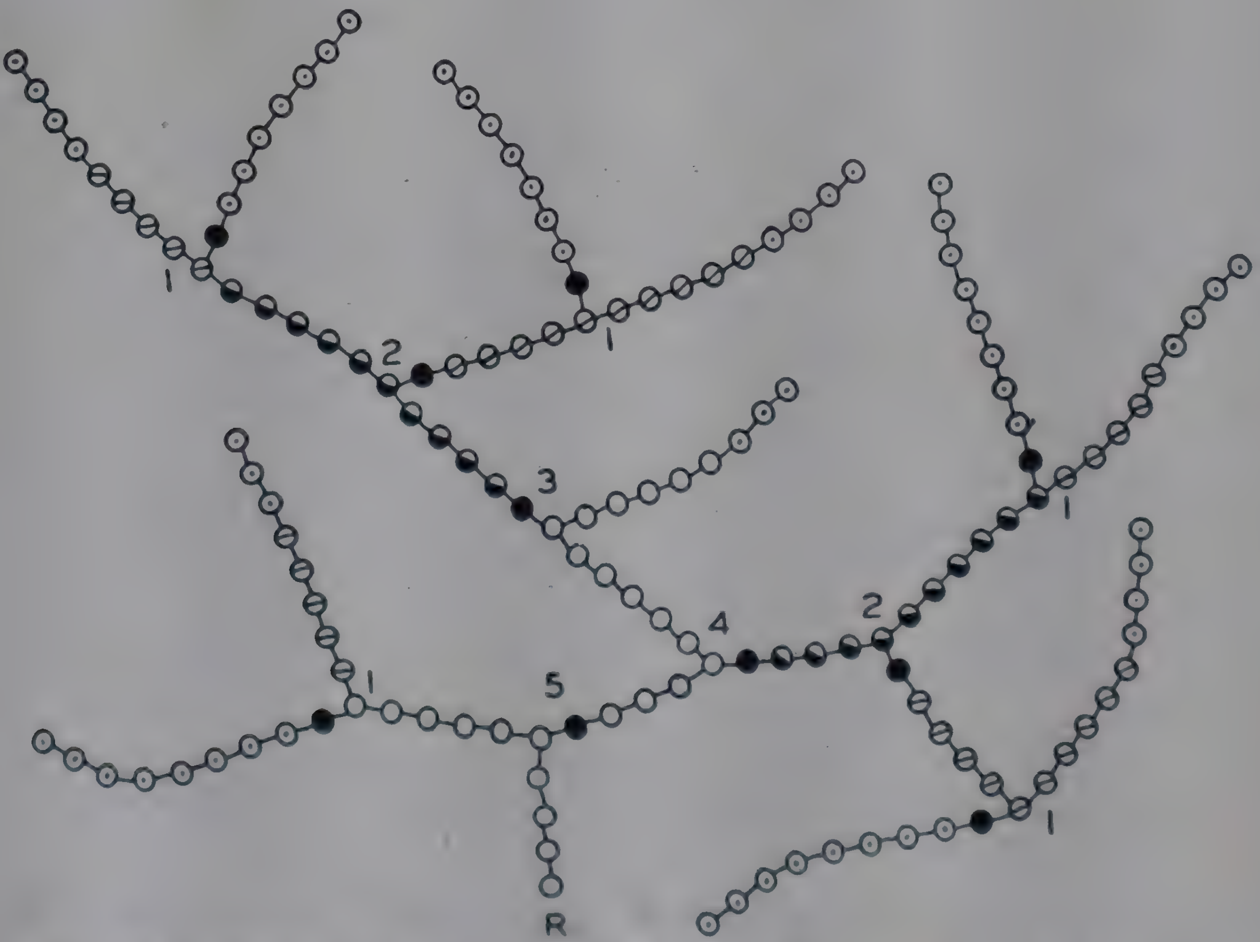


FIG. 19. A diagrammatic structure of glycogen. R, reducing end of molecule. ⊙, ⊖, ◒, glucose units removed by the first, the second and the third digestions with phosphorylase. ● Glucose unit split off as free glucose from 1, 6 linkage by amylo-1,6-glucosidase. (From data of Larner and G. T. Cori, according to B. Glass in W. D. McElroy and B. Glass, Phosphorus Metabolism, vol. I, p. 667, Baltimore, Johns Hopkins Press)

noved from glycogen one unit at a time as lucose-1-phosphate. The latter compound is onverted to glucose-6-phosphate by the enyme phosphoglucomutase. Then glucose-6-hosphate is hydrolyzed in the presence of lucose-6-phosphatase, an enzyme present in igh concentrations in the liver, to yield lucose. By these reactions the liver can nake glucose into glycogen which can be tored. When necessary the glycogen can be plit to glucose for further use.

In one kind of glycogen storage disease (Von Gierke's disease) there is a deficiency n the liver of the enzyme glucose-6-phosphaase. Its absence prevents the rapid breaklown of liver glycogen. The clinical results re (1) hypoglycemia, (2) the flat bloodlucose curve after epinephrine injection, (3) the accumulation of glycogen in the liver nd (4) the absence of postmortem disapearance of glycogen.

As mentioned above, the straight chains of glucose have 1,4 linkages. These chains re held together by 1,6 linkages. The strucure of glycogen is not a straight chain but s treelike with arborization (Fig. 19). Whereas phosphorylase is specific for the 1,4 inkages in the chain, the branching points or 1,6 linkages require the enzyme 1,6-glucosidase. In the process of glycogenolysis, phosphorylase can split off glucose (1,4 inks) down to the site of the branching, whereupon the 1,6-glucosidase breaks the branch (1,6 links) leaving straight chains. The phosphorylase continues its action ntil another branch is reached. With the se of labeled glucose it has been shown that glucose may join or leave the periphery of a glycogen molecule while the central porion remains intact.[36] Cori[9] has estimated hat for every 15 glucose units in glycogen one is 1,6 linked and 14 are 1,4 linked. He cites a case of Von Gierke's disease in which he glycogen was different in that it had fewer branches, indicating fewer 1,6 links and onger straight chains.

ENDOCRINE FACTORS THAT AFFECT GLUCOSE OR GLYCOGEN PRODUCTION

In order to provide the brain and other issues with a continuous supply of vitally eeded glucose the liver must be able to ontrol its glucose output and also to store glucose as glycogen. Two factors which increase the rate of glycogen breakdown to glucose are epinephrine and the hyperglycemic factor of the pancreas. When epinephrine is injected into man or experimental animals a rapid breakdown of liver and muscle glycogen occurs with a rise in blood sugar and lactic acid. This response has been used as a clinical test. When the hyperglycemic factor is injected a similar response is obtained. Recently Van Itallie et al.[38] injected both hyperglycemic factor and epinephrine and correlated the rise of blood glucose with liver function. The epinephrine was used presumably to cause vasoconstriction and reduce peripheral glucose utilization temporarily, as well as for its glycogenolytic action. Also, epinephrine may act by stimulating the pituitary to produce ACTH, which then activates the adrenal to secrete its steroids, some of which are gluconeogenic. It appears to act directly in the liver and in muscle too on the balance between synthesis and destruction of phosphorylase, to shift the balance in favor of resynthesis of active phosphorylase. The hyperglycemic factor seems to act on phosphorylase in a similar manner. The change from inactive to active phosphorylase can lead to a doubling of activity in the liver within a few minutes.[37]

Glycogen synthesis in muscle is increased by the presence of insulin, and this effect has been stated to be on the glucokinase system where glucose-6-phosphate is made.[25] Pituitary or adrenal extracts are said to decrease the rate of formation of glucose-6-phosphate from glucose and ATP by inhibiting glucokinase. Insulin is supposed to release this inhibition and thereby allow the formation of glucose-6-phosphate at a greater rate. The pituitary factor appears to be related to crystalline growth-hormone, while adrenal activity seems to be the potentiation of the growth-hormone inhibition of hexokinase.[23] The net effect of insulin action is to push the glucose to glycogen. This mechanism is doubted by many biochemists. Potassium appears to be related in some manner. Conditions which maintain the intracellular potassium at normal concentrations favor glycogen formation from glucose and pyruvate, whereas a decrease of potassium decreases glucose uptake by the liver slice but favors the conversion of pyruvate to glucose.[16] The relationship of these facts to liver function is obscure. However, it should be noted that many patients with hepatic coma tend to become potassium deficient and clinically worse when not supplemented with potassium.

HYPOGLYCEMIA

In the fasting state the blood leaving the liver always must carry more glucose than the blood entering or hypoglycemia will develop. In starvation, where liver glycogen is not being replaced, the blood glucose falls. If liver glycogen forms adequately but does not break down rapidly enough as in hyperinsulinism or in Von Gierke's disease hypoglycemia develops. No deficiency of epinephrine has been demonstrated where glycogenolysis was retarded, nor has a pancreatic deficiency of hyperglycemic factor with similar effect been demonstrated. Frequently, pituitary and adrenal insufficiency are associated with hypoglycemia because of the unopposed effect of insulin, although starvation also may be a contributory cause here. Hypoglycemia is treated with glucose or amino acids (proteins) which can go to glucose.

The associated lipemia, ketosis and acidosis are related to an increase in fat metabolism in the liver. This leads to an increase of the acetate pool and an increase of acetoacetic acid. The ketosis will be discussed below.

METABOLISM OF OTHER SUGARS RELATED TO GLUCOSE

Fructose is metabolized readily by the liver; a fructokinase is present in the liver which catalyzes the phosphorylation to fructose-6-phosphate which can enter the Embden-Meyerhof scheme (Fig. 24) and then go to 1,6-fructose-diphosphate and so on. In rat liver homogenates fructose is phosphorylated 10 times as fast as glucose. Furthermore, fructokinase functions independently of the pituitary factor or insulin. This explains the ability of the diabetic liver to utilize fructose readily when it is not using glucose normally. As noted above, glucokinase is said to be sensitive to the pituitary factor and to insulin. Fructose-1-phosphate can be converted to glucose and glycogen in the liver.

A galactokinase has been reported in liver which leads to the conversion of galactose to galactose-1-phosphate. A new coenzyme, uridine-diphosphate-glucose (UDG), with the aid of some incompletely established enzymes, reacts with galactose-1-phosphate to form glucose-1-phosphate. When C^{14}-labeled galactose in the 1 position was fed to rats, most of it was found in the 1 position of glucose incorporated into glycogen, suggesting that this system is present in liver and that the intact carbon chain of galactose is used to make glucose.

Infants and children who suffer from galactose intolerance do not convert galactose to glucose adequately perhaps because of a deficiency in liver of galactokinase or galactowaldenase, the enzymes which facilitate phosphorylation and conversion of galactose to glucose. High blood and urine galactose values are found with low blood glucose levels. Since the major source of carbohydrate for the infant is milk, the sugar provided is lactose which is split in the intestines to glucose and galactose. The glucose is handled in the usual manner, but the galactose is not. Avoidance of lactose in this biochemical disease is of decided benefit.

THE AEROBIC SHUNT AND THE CONVERSION OF HEXOSES TO PENTOSES

As shown above, the hexoses are converted eventually to glucose. Glucose in turn can be converted to pentoses which are utilized as such or further oxidized. This mechanism shown now in most biologic systems has been named the aerobic oxidative pathway, glucose shunt or the Warburg-Dickens scheme.[7] In liver glucose-6-phosphate-dehydrogenase oxidizes glucose-6-phosphate to the delta-gluconolactone with DPN (ox) or TPN (ox) as the oxidant. Gluconolactone can be hydrolyzed to gluconic acid. Oxidation to ketogluconic acid and then decarboxylation to ribose-phosphate leads to the pentoses ribulose and ribose. This may be the pathway by which the liver synthesizes ribose, which is utilized in the building of many important compounds in liver (DPN, TPN, FAD, ATP and nucleic acids). Some

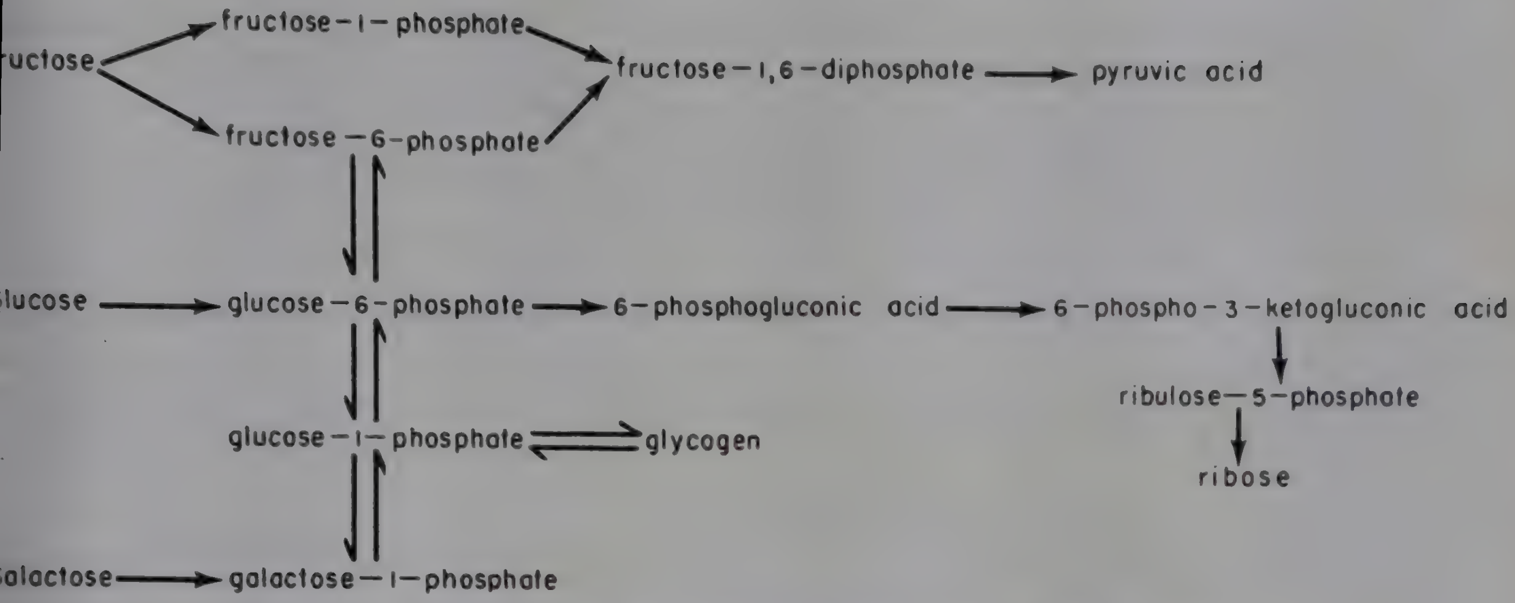

uctose
fructose-1-phosphate
fructose-6-phosphate
fructose-1,6-diphosphate
pyruvic acid
lucose
glucose-6-phosphate
6-phosphogluconic acid
6-phospho-3-ketogluconic acid
ribulose-5-phosphate
ribose
glucose-1-phosphate
glycogen
alactose
galactose-1-phosphate

FIG. 20. Summary of the metabolic pathways of the hexoses. (Modified from White et al.[42])

evidence is accumulating that this alternate glucose pathway may be the major pathway of glucose in the liver, as indicated by the presence of the needed enzymes and by the fact that 75 per cent of glucose can be oxidized in the intact rat by a pathway resembling the shunt mechanism.[5]

The meaning of this scheme in liver disease is even more obscure. Smith et al.[34] noted as many before them that glucose given intravenously yields little or no change in blood pyruvate, whereas fructose produces a marked rise in pyruvate. Previous explanations suggested that fructose entered the gly-

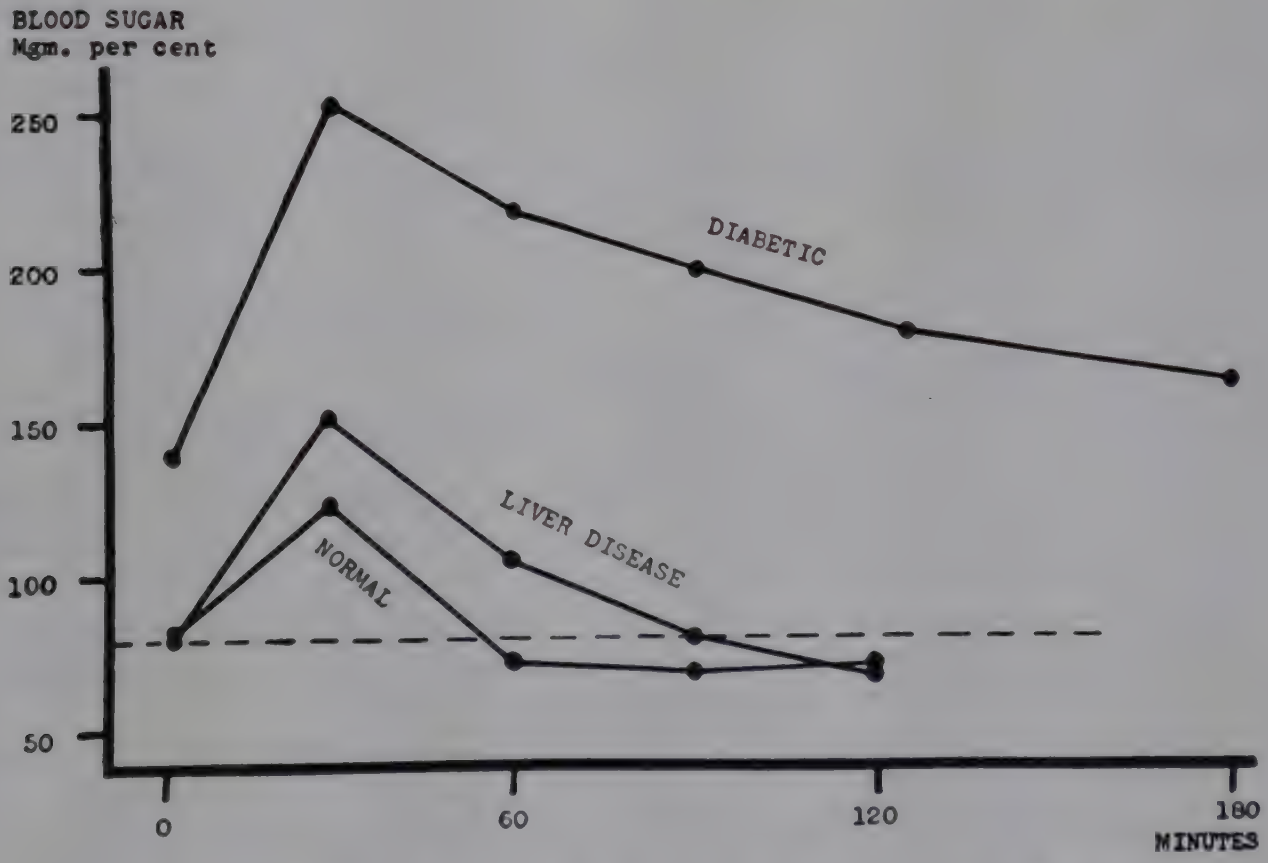


FIG. 21. The average intravenous dextrose tolerance curves of 30 normal, control individuals; 25 of the mildest cases of diabetes mellitus which were available; and 50 cases of proved mild or early liver disease. The normal curve returns to the preinjection level by 60 minutes, the hepatic curve returns after 60 and before 120 minutes, the diabetic curve returns after 120 minutes. (From Soskin[35])

colytic scheme via fructokinase to fructose-diphosphate to pyruvate, whereas glucose had to go a step or two more to reach pyruvate. The suggestion offered is that glucose normally may be oxidized to a large extent via the aerobic pathway and yield less pyruvate than fructose, which goes via the Embden-Meyerhof scheme, which yields considerably more pyruvate.

Figure 20 summarizes the interrelationships of the sugars.

CARBOHYDRATE TOLERANCE TESTS IN THE STUDY OF LIVER DISEASE

Since the liver handles carbohydrates to such a large extent it would seem reasonable to believe that in disease this ability might diminish. A glucose tolerance test is abnormal in many cases of liver disease. Figure 21 shows curves obtained in glucose tolerance tests of the normal patient and those with liver disease or diabetes. The fasting blood glucose is normally 70 to 100 mg. per cent. When one third Gm. of glucose per kilo of body weight is injected, a rise of blood glucose occurs. The ability of the liver and muscle to remove glucose is reflected in these curves. In the liver disease case the rise is rapid and short-lived. No insulin defect is thought to be related. If the amount of glucose administered exceeds peripheral utilization, the test probably measures the ability of the liver to utilize glucose. Unfortunately, the many factors involved are difficult to control. It would seem that the glucose intolerance of liver disease (insulin factor omitted) is related to (1) circulation, (2) adequate hexokinase, (3) adequate amount of ATP and (4) adequate pathway below phosphorylated glucose. In the oral test in severe liver disease, the altered circulation allows the portal blood to shunt past the liver and reach the periphery first, whereupon it subsequently reaches the liver via the hepatic artery. The elevated glucose stimulates the pancreas to secrete insulin, which stimulates the muscles and the liver to remove glucose, thereby making the hyperglycemia short-lived. In the diabetic the liver and peripheral tissues cannot utilize glucose at these normal rates, so that a load of glucose entering the body will circulate longer and lead to higher blood levels than normal. In a malfunctioning liver it seems most likely that there would be a deficiency of the glucose-utilizing enzymes, and for that matter an over-all deficiency of enzymes of other systems such as the citric acid cycle. Usually, enzymes are present in abundance, however, so that a decrease in liver enzyme concentration might not cause a significant fall in glucose utilization during the glucose tolerance test. A more significant deficiency might exist in the high-energy-phosphate pool (ATP). This pool is built up, in the main, by the oxidation in the citric acid cycle and other oxidative schemes. If this cycle should be deficient, as may be the case, the ATP reservoir might be diminished, and in such event the phosphorylation of glucose to glucose-phosphate could well be limited and thereby lead to the glucose intolerance of liver disease. Therapy with ATP is useless, because phosphatases would hydrolyze it before it could reach the vital points of the cells. The only way to combat this defect is to replenish the ATP pool. The glucose intolerance of starvation is abolished by feeding. This may be due to the building up of the ATP pool in the liver.

If glucose is utilized it is presumed that phosphate also should be utilized, so that a simultaneous drop of phosphate in serum should accompany the rise of blood glucose. It was proposed that this fall is characteristic for liver disease as compared with that for diabetes.[12] However, this does not seem to be consistently true in the differentiation of the glucose tolerance of liver disease from that of diabetes.

The fructose tolerance test has been reported to measure liver function. Fructose does not require insulin for utilization; hence, the capacity of the liver to utilize fructose is a reflection of liver function. Theoretically, this might seem to be a better carbohydrate tolerance test. Actually, it has provided little clinical help.

The galactose tolerance test undoubtedly correlates with liver function.[2] As shown above, galactose is phosphorylated to galactose-1-phosphate and then is converted to glucose-1-phosphate through the uridine transfer. The mechanism of the intolerance might be related to a decreased galactokinase, ATP reservoir, waldenase or uridine-diphosphate carrier in the liver.

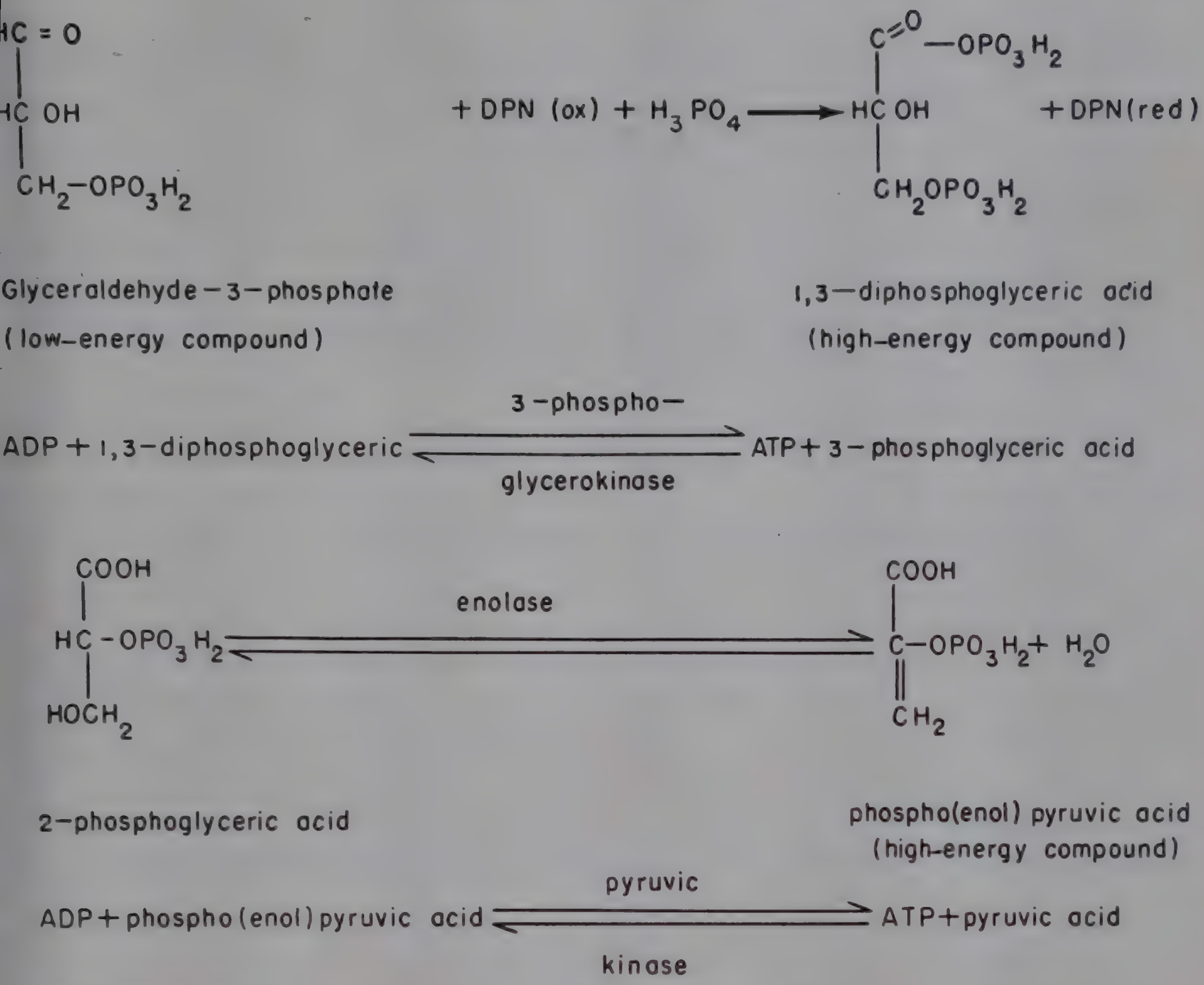

Glyceraldehyde-3-phosphate
(low-energy compound)
+ DPN (ox) + H3PO4
+ DPN (red)
1,3-diphosphoglyceric acid
(high-energy compound)
ADP + 1,3-diphosphoglyceric
3-phospho-
glycerokinase
ATP + 3-phosphoglyceric acid
enolase
2-phosphoglyceric acid
phospho(enol) pyruvic acid
(high-energy compound)
ADP + phospho(enol) pyruvic acid
pyruvic
kinase
ATP + pyruvic acid

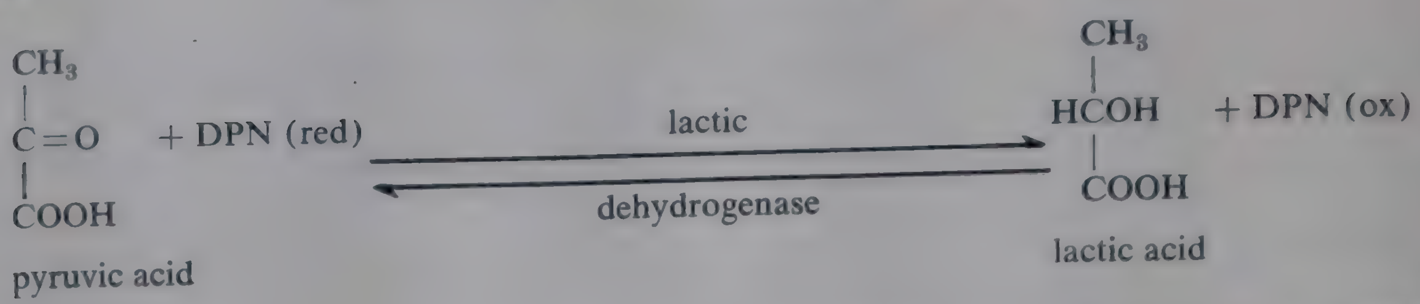
FIG. 22. Oxidative reactions of glycolysis which produce high-energy phosphate bonds and then ATP.

THE EMBDEN-MEYERHOF SCHEME OR ANAEROBIC GLYCOLYSIS

Glycolysis and Oxidative Phosphorylation. The pathways leading to fructose, 1,6-diphosphate have been described and diagrammed. This molecule is split into two 3-carbon fragments, dihydroxyacetone-phosphate and glyceraldehyde-3-phosphate, by the enzyme aldolase. These 3-carbon compounds are isomers and can be converted to one another by the enzyme phosphotriose isomerase. Reduction of dihydroxyacetone-phosphate in the presence of the proper dehydrogenase by TPN produces glycerophosphate which on hydrolysis yields glycerol. By this mechanism the liver probably makes glycerol for fat synthesis.

The major reaction, however, is the oxidation of glyceraldehyde-3-phosphate to the corresponding glyceric acid and the simultaneous phosphorylation of the acid group to form 1,3-diphosphoglyceric acid (Fig. 22). The enzyme involved is phosphoglyceraldehyde dehydrogenase, and DPN (ox) is the oxidant. It is important to note that the energy released in the oxidation of the aldehyde is incorporated into the high-energy content of the new acyl-phosphate bond. This compound can react with adenosine-diphosphate in the presence of 3-phosphoglyceric kinase to form adenosine-triphosphate, another high-energy compound (Fig. 22). The latter (Fig. 23) may be the major reservoir for storing or supplying high-energy phosphate for the numerous synthetic reactions of the liver.

The sum total of these reactions is that oxidation of 3-phosphoglyceric acid leads



$$\underset{\text{pyruvic acid}}{\begin{array}{c}CH_3\\|\\C=O\\|\\COOH\end{array}} + \text{DPN (red)} \xrightleftharpoons[\text{dehydrogenase}]{\text{lactic}} \underset{\text{lactic acid}}{\begin{array}{c}CH_3\\|\\HCOH\\|\\COOH\end{array}} + \text{DPN (ox)}$$

to the production of an equivalent amount of ATP, which provides the energy for other reactions, of which the phosphorylation of glucose is an example. This is a demonstration of coupled oxidation and phosphorylation which leads to the incorporation of the energy of oxidation into a phosphate bond and subsequently ATP.

The 3-phosphoglyceric acid can be converted into 2-phosphoglyceric acid by the enzyme phosphoglyceromutase. The 2-phosphate ester is dehydrated in the presence of the enzyme enolase to yield phospho(enol)-pyruvic acid, with the resultant conversion of a low-energy-phosphate ester to a high-energy ester (Fig 22). This new compound also can convert ADP to ATP. This is another example of high-energy-phosphate-bond synthesis. The enol at the pH of body fluids rapidly goes to the keto form, which is pyruvic acid. Reduction of pyruvic acid by DPN (red) in the presence of lactic dehydrogenase forms lactic acid.

In muscle or anaerobic systems lactic acid accumulates. The lactic acid that arises in peripheral tissues or liver can be converted in liver, although not in muscle, all the way back to glucose or glycogen because all the necessary enzymes are present, and all the steps are essentially reversible. In man an arteriovenous difference of lactate occurs across the liver, indicating the normal use of lactate by the liver. Figure 24 summarizes the series of reactions and the enzymes involved in the conversion of glycogen to lactic acid or vice versa. For each mole of glucose which is oxidized anaerobically to lactic acid, 2 moles of ATP are con-

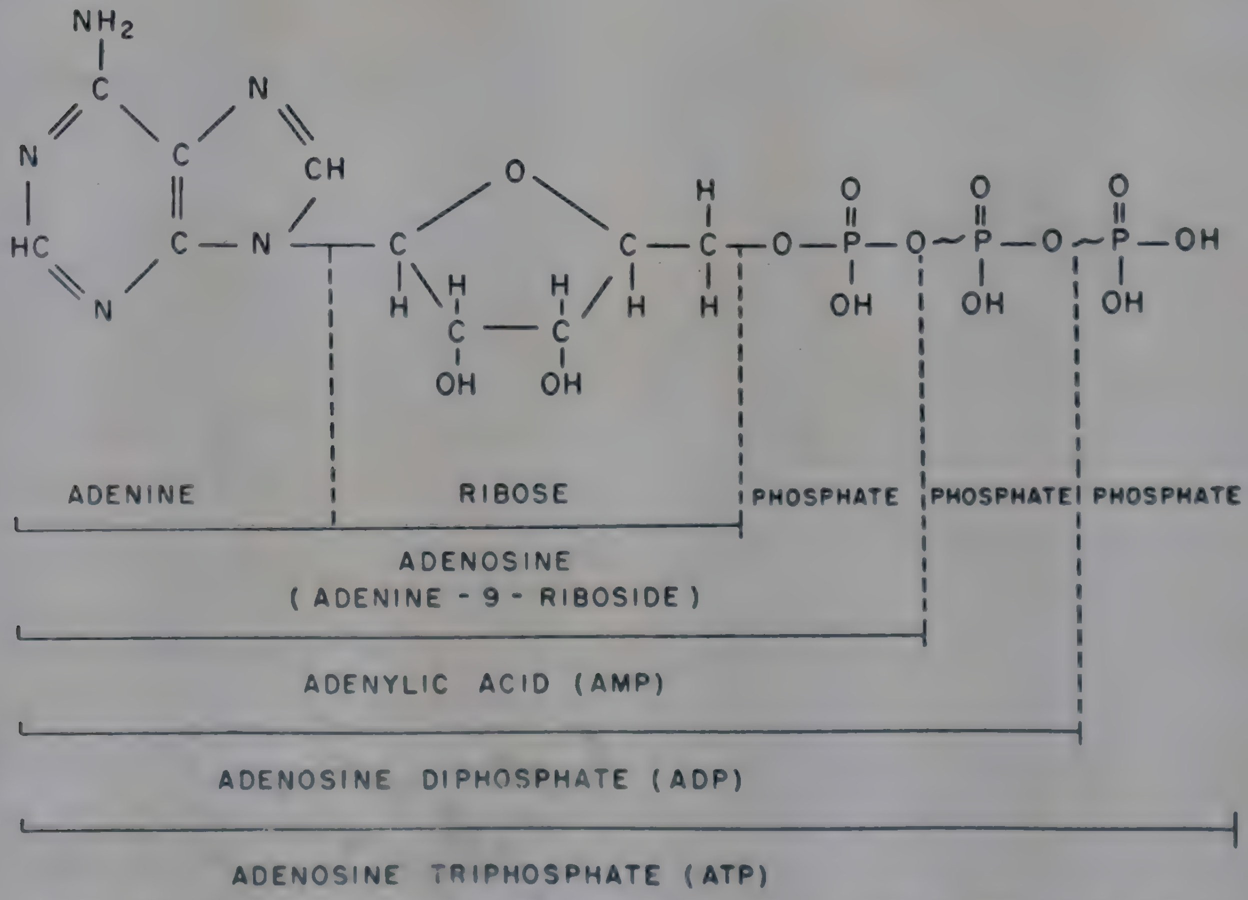

ADENINE
RIBOSE
PHOSPHATE
PHOSPHATE
PHOSPHATE
ADENOSINE
(ADENINE - 9 - RIBOSIDE)
ADENYLIC ACID (AMP)
ADENOSINE DIPHOSPHATE (ADP)
ADENOSINE TRIPHOSPHATE (ATP)

FIG. 23. The structure of adenosine-triphosphate (ATP). (From B. Glass, in W. D. McElroy and B. Glass, Phosphorus Metabolism, vol. I, p. 662, Baltimore, Johns Hopkins Press)

sumed, and 4 are regenerated, resulting in a net gain of 2 moles of ATP from the glycolysis of 1 mole of glucose. If the reaction starts with glycogen the net gain is 3 moles of ATP per theoretical mole of glucose.

This system of reactions for glycolysis has been referred to as the Embden-Meyerhof pathway.

Pyruvic acid is an unusually active substance and fits into many pathways. As mentioned, pyruvate may be reduced to lactate, which is a considerably less active compound and has to be reoxidized to pyruvate in order to enter the metabolic pools. Phosphorylation of the enol of pyruvate allows it to go through any or all of the reactions up to glycogen. Pyruvate can be carboxylated and ultimately yield the key compound oxalacetate. Pyruvate after decarboxylation yields acetyl CoA (Fig. 28) which can be oxidized

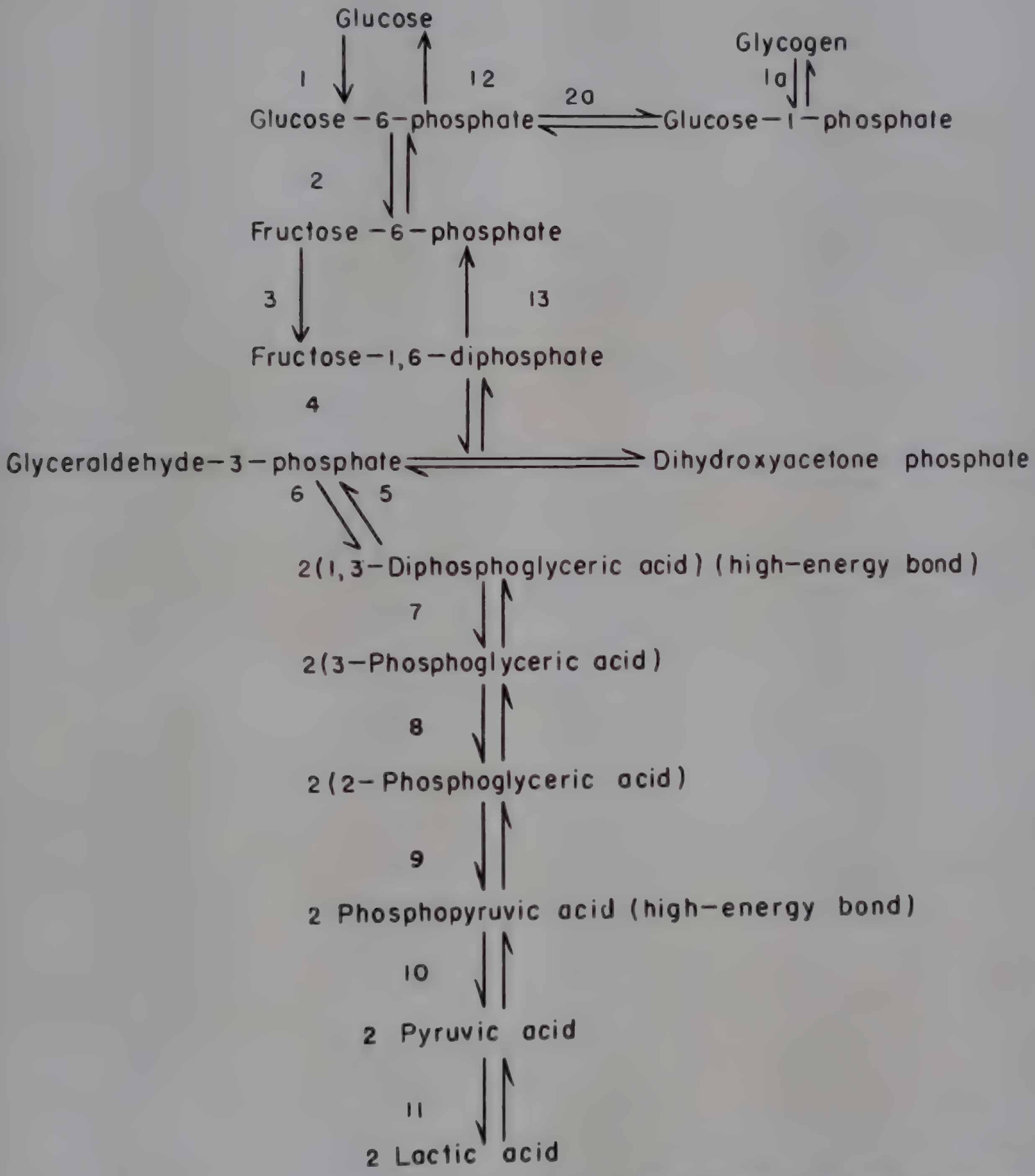

Glucose
1
12
Glycogen
1a
2a
Glucose-6-phosphate
Glucose-1-phosphate
2
Fructose-6-phosphate
3
13
Fructose-1,6-diphosphate
4
Glyceraldehyde-3-phosphate
Dihydroxyacetone phosphate
6
5
2(1,3-Diphosphoglyceric acid) (high-energy bond)
7
2(3-Phosphoglyceric acid)
8
2(2-Phosphoglyceric acid)
9
2 Phosphopyruvic acid (high-energy bond)
10
2 Pyruvic acid
11
2 Lactic acid

FIG. 24. Summary of reactions between glycogen to lactic acid. The numbers refer to the following involved enzymes: (1) hexokinase, (1a) phosphorylase, (2) phosphohexose isomerase, (2a) phosphoglucomutase, (3) phosphofructokinase, (4) aldolase, (5) phosphotriose isomerase, (6) phosphoglyceraldehyde dehydrogenase, (7) phosphoglyceric kinase, (8) phosphoglyceromutase, (9) enolase, (10) phosphopyruvic kinase, (11) lactic dehydrogenase, (12) glucose-6-phosphatase, (13) diphosphofructose phosphatase. (Modified from White et al.[42])

to CO_2 and water in the citric acid cycle and in the process yield more energy than the glycolytic scheme which produced the pyruvate. The decarboxylation requires the presence of thiamine-pyrophosphate (cocarboxylase), lipoic acid (a new growth factor of known structure), and magnesium or manganese ions. In thiamine deficiency in animals or man (beriberi) the decarboxylation is impaired, and pyruvic acid accumulates in the blood and the urine. Undoubtedly, the liver is affected in this deficiency. This reaction which forms acetyl CoA links carbohydrate and fat metabolism. The acetyl CoA can be synthesized into fatty acids, which explains how the feeding of carbohydrate produces fat deposition.

By the process of reductive amination pyruvic acid can yield the amino acid alanine, thus linking carbohydrate and protein metabolism.

OXIDATION IN THE LIVER

The Oxidative Chain

The process of oxidation is the major source of energy for the liver and for the body in general. Some of the energy so derived is dissipated as heat, but the majority is stored in chemical bonds which allow reactions to proceed that are vital to life. Most of the energy formed is stored in the compound ATP which can be made available for many of the synthetic reactions of the liver. For example, the energy of oxidation is necessary for the synthesis of urea from ammonia, which results from the metabolism of proteins. A failure of oxidation can lead to a failure of ATP synthesis and as a consequence a failure of urea synthesis. This results in the accumulation of ammonia, an extremely toxic substance. This perhaps is the situation in hemorrhagic shock where hypoxia in the liver leads to the accumulation of ammonia in the blood.[22] The nature of 2 mechanisms of coupling of oxidation to high-energy-bond formation has been mentioned. The fact that the liver is extremely sensitive to hypoxia or enzyme deficit indicates how vital reactions are dependent upon the energy from oxidation.

Many of the chemical reactions of the liver which have been demonstrated have been studied in vitro in the Warburg apparatus where oxygen consumption and CO_2 production are measured. The microliters of oxygen taken up by a milligram of dry tissue in 1 hour is called the $-QO_2$. Rat kidney slices may have a $-QO_2$ of 21 as compared with liver where the $-QO_2$ may be 15. Although the kidney may have a higher respiratory rate, the total oxidative capacity as compared with the liver is low.

Oxidation in the older sense means combination with oxygen, a process which does occur in animal tissues to some degree. However, other ways of oxidation are possible and more common. Oxidation is better defined as the removal or withdrawal of electrons from the substance being oxidized, while reduction is the addition or gain of electrons. When lactic acid is oxidized as previously shown, some compound must accept the hydrogen and electrons and thereby be reduced in the process. As will be discussed later, this compound that is reduced during lactate oxidation in the liver is diphosphopyridine nucleotide. It should be emphasized that the enzyme in this case does not oxidize the lactic acid; it catalyzes the reaction so that equilibrium is reached more rapidly. In this example DPN (ox) is the oxidizing agent, and in the process of accepting the hydrogen and electrons it becomes reduced.

In most of the reactions in biologic systems the electrons and hydrogen which are removed in oxidation are transferred to carriers such as DPN in the example cited above. Then the electrons may be transferred to other carriers and finally to oxygen. The simultaneous passage of hydrogen and electrons on to molecular oxygen produces water. The carrier functions between two oxidation-reduction systems to allow the reduced form of one to react with the oxidized form of the other. The 3 groups of known carriers in the liver are the pyridine nucleotides, the flavin nucleotides and the cytochromes. It is believed that other systems exist. Each respiratory enzyme consists of a specific protein with a coenzyme or prosthetic group. The protein activates the substrate and prosthetic group in a specific manner so that they will react easily. There are a multitude of specific enzymes for the various substrates but only a small number of coenzymes. Table 1 lists the known coenzymes and the vitamins which make them up. Practically all of these dehydrogenations occur in the liver as well as in other tissues.

PYRIDINE NUCLEOTIDES

The pyridine nucleotides are of great importance in biochemical reactions. Many of the important known oxidations begin by the passage of electrons from the substrate to a pyridine nucleotide. Reduced DPN or TPN has a distinct absorption band at 340 μ in the spectrophotometer which disappears when oxidation occurs. Measurement of the change of light absorption of these compounds during an oxidation or reduction in the spectrophotometer provides an analytical tool for many different kinds of analyses in which a substrate is oxidized or reduced in the presence of these cofactors.

Two main pyridine nucleotides are catalytically active in the cells. Diphosphopyridine nucleotide is known as coenzyme I (Co I) or cozymase and is abbreviated as DPN (Fig. 25). The oxidized form is abbreviated as DPN+ or DPN (ox) and the reduced form DPNH or DPN (red). It is here that the vitamin nicotinic acid or nicotinamide is essential. Triphosphopyridine nucleotide, known as coenzyme II or codehydrogenase II and abbreviated as TPN, differs from DPN by having another phosphate ester group. The pyridine part of the nicotinamide participates in the oxidation-reduction by accepting or passing on hydrogen and electrons. With transfer of a pair of electrons and a hydrogen atom to the pyridine ring reduced DPN may be reoxidized by the appropriate pyridine dehydrogenase in the presence of substrate or by certain flavoproteins which are specific for a particular pyridine nucleotide (cytochrome reductases). The DPN content of liver is about 1 mg. per Gm. or 0.1 per cent. TPN is present to a lesser extent. The reservoir of DPN is small. If it is to participate in oxidations it must quickly pass on its hydrogen and electrons to other acceptors. This versatility and participation in a wide variety of reactions makes these compounds exceedingly important in cellular metabolism.

DEHYDROGENASES

A compound such as ethyl alcohol is oxidized readily by the liver. The oxidation is achieved by passage of electrons and hydrogen from alcohol to DPN.

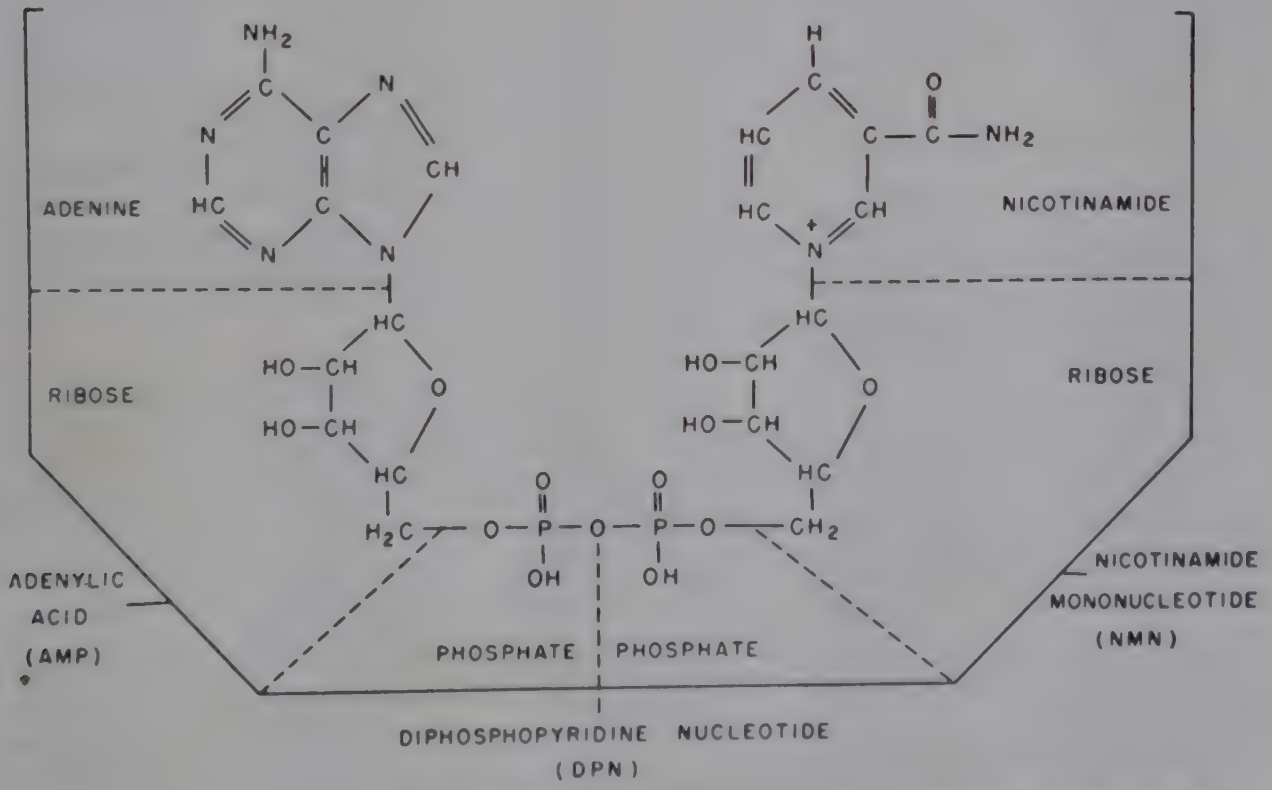


FIG. 25. The structure of diphosphopyridine nucleotide (DPN). (From B. Glass, in W. D. McElroy and B. Glass, Phosphorus Metabolism, vol. I, p. 663, Baltimore, Johns Hopkins Press)

$$\text{DPN (ox)} + CH_3CH_2OH \xrightarrow[\text{dehydrogenase}]{\text{alcohol}} CH_3CHO + \text{DPN (red)}$$

The oxidation will not occur in a test tube containing DPN (ox) and alcohol. When the crystalline enzyme, alcohol dehydrogenase, is added the reaction proceeds rapidly. The reaction proceeds further when catalyzed by another enzyme aldehyde dehydrogenase, again with DPN as the carrier or oxidant. Horse liver contains a large amount of this enzyme (1 Gm. per kilo).

$$CH_3CHO + H_2O + \text{DPN (ox)} \xrightarrow[\text{dehydrogenase}]{\text{aldehyde}} CH_3COOH + \text{DPN (red)}$$

To what extent the diseased liver with distorted anatomy fails in this type of integration is unknown. The removal rate of alcohol by the diseased liver is less than normal. Whether this is the result of loss of functioning liver tissue per unit of body weight, or to a disruption of the integrated chain of events in the liver cell, or both, is yet to be defined clearly.

The rate of alcohol oxidation in vivo, as described by the velocity constant of the alcohol dehydrogenase reaction, is about 10 times that observed for the in vitro system using crystalline enzyme. The oxidation in the liver is facilitated by the presence of the necessary cofactor and associated enzyme systems which allow continuous removal of reaction products and continuous regeneration of DPN (ox). The integration of chemical functions is suggested by this increased rate of oxidation. The micro-anatomic integration presumably accounts for this chemical integration.

A host of such dehydrogenases exists in liver, and their carriers are DPN or TPN. Some of these will be mentioned in the discussion of the oxidation of specific compounds.

FLAVIN NUCLEOTIDES AND FLAVOPROTEINS

The next group of electron carriers is the flavin group represented by riboflavin, which is easily oxidized or reduced. It has a higher oxidation potential (E_0 is -0.180 volts), which means it is in a higher state of oxidation than the pyridine nucleotides and can accept electrons from the latter. In the process riboflavin is reduced, and the pyridine nucleotide is oxidized. The functioning coenzyme is flavin adenine dinucleotide (FAD), the prosthetic group of most of the riboflavin-containing enzymes. These enzymes have been shown in many cases to be metalloproteins containing molybdenum, copper or iron. These metals facilitate the passage of electrons to and from the substrate. There are flavin enzymes which accept electrons from DPN (red) (oxidation of DPN), and there are flavin enzymes which accept electrons directly from the substrates (oxidation of substrate).

When FAD adsorbs on the protein its E_0 is -0.05 volts, which is more positive or in a higher state of oxidation than unbound riboflavin. This is more like what it is in the liver.

More than a dozen flavoprotein enzymes have been studied. Of these xanthine oxidase, aldehyde oxidase and cytochrome c reductase have been reported in the liver. Others undoubtedly exist there too. In the cell the reduced flavoproteins are oxidized by cytochromes, which continue the chain of oxidation by accepting electrons from the flavoproteins.

CYTOCHROMES AND CYTOCHROME OXIDASE

The cytochromes or cell pigments are porphyrins containing iron linked to a protein.

Three cytochromes isolated from tissues manifest characteristic spectral-absorption bands; these are cytochrome a, b and c, of which the most studied is cytochrome c. It is contained in all aerobic tissues. The liver contains about 100 micrograms per Gm. of tissue. The heart contains approximately 3 times this quantity, while the brain and muscle contain half this amount.

he iron in the molecule allows it to undergo eversible oxidation or reduction. ($Fe^{++} \rightleftharpoons e^{+++} + e$, $E_o = +0.26$ volts.) At this igh level of oxidation cytochrome c can oxi-ize the flavoproteins readily. The enzyme ytochrome oxidase catalyzes the oxidation f reduced cytochrome by atmospheric oxy-en. By the use of enzyme inhibitors cyto-hrome oxidation may be blocked. From uch experiments it has been estimated that t least 60 per cent of oxidation in animal ells occurs over the electron-carrying chain, tarting with substrate, going to DPN, to avin nucleotide, to cytochrome c, to oxy-en. This chain is shown in an example Fig. 26) taken from White et al.[42] for the xidation of β-hydroxybutyrate to acetoace-ate where the electrons and hydrogen are assed up the chain. At the other end oxygen s activated by cytochrome oxidase. In this ashion oxygen with an E_o of +0.81 can xidize β-hydroxybutyrate with the E_o of –0.29, as shown. Cytochrome c is shown s the example for the whole group of ytochromes.

This chain of events can produce hydro-en peroxide, a toxic substance. All tissues ontain large amounts of the enzyme cata-ase, a special kind of peroxidase, which acilitates the rapid breakdown of the eroxide ($2H_2O_2 \longrightarrow 2H_2O + O_2$), nd prevents the toxic effects of this com-ound. Aside from the breakdown of H_2O_2 y catalase its role in the liver is unknown. t may play a more important role in sub-trate oxidation than is now apparent. The xidative chain shown in Figure 26 is present n the mitochondria of liver tissue and other rgans.

The operation of this chain clarifies an-erobic oxidation as it occurs in the oxida-ion of ethyl alcohol to acetic acid and also erobic oxidation which occurs with oxygen onsumption. Vitamin deficiencies of nico-nic acid (or amide) or of riboflavin affect ne first part of this chain. Enzyme inhibitors ich as carbon monoxide, cyanide, azide and ydrogen sulfide form complexes with the on-cytochrome or copper-protein enzymes r compete with oxygen by combining with ie porphyrin and interfere with the oxida-ve chain at the terminus.

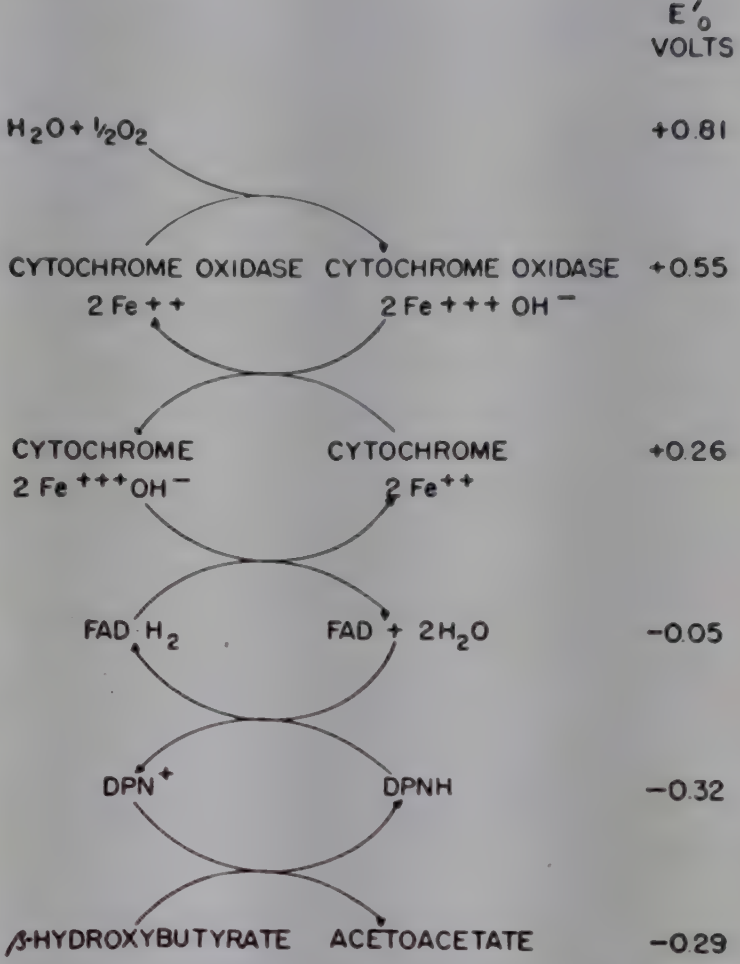


FIG. 26. The oxidative chain or sequence of reactions in the anerobic oxidation of β-hydroxybutyric to acetoacetic acid. DPN (ox) in the presence of the dehydrogenase enzyme oxidizes the substrate by accepting 2 hydrogen atoms and 2 electrons and in the process is reduced. In turn the electrons and hydrogen are passed up the chain as shown, ultimately reacting with oxygen. (From White et al.[42])

The basic concept introduced in the study of oxidations is that the energy released in the respiratory oxidative scheme is coupled with high-energy-bond synthesis. Although different types of reactions are involved it is ATP that accumulates as shown above. The ATP is the driving force for many synthetic reactions and specialized tissue functions. It is the so-called "unit of currency" in metabolic systems. Continued oxidation of the reduced coenzymes which result from fat and carbohydrate metabolism produce the stepwise liberation of the energy which is incorporated into the high-energy bonds. In this manner the tissues burn carbohydrate or fat with oxygen from the air and accumulate the energy in high-energy compounds rather than as heat.

AEROBIC OXIDATION VIA THE CITRIC ACID CYCLE

The ultimate metabolism of carbohydrates, proteins and fats yields 2-, 3-, 4- and 5-carbon fragments which enter a common metabolic pool for further oxidation to CO_2 and water (Fig. 27). Much of the resultant energy produced is incorporated into ATP. The series of reactions involved occurs in a cyclic, regenerative manner so that the components of this cycle are renewed constantly. Even though these chemical components are present in relatively small quantities,* the oxidative capacity of this metabolic cycle is great and of importance in the intact animal. The withdrawal of some of these components, as will be mentioned below, can lead to a reduced capacity of the cycle with consequent diminished production of ATP and failure of ATP-dependent reactions. This series of reactions has been labeled the citric acid cycle, the tricarboxylic acid cycle, the TCA cycle and the Krebs cycle after the man who described it.

The citric acid cycle is currently understood as shown in Figure 27, which shows the relationship between fatty acid and carbohydrate metabolism and the citric acid cycle. The key reaction involves the condensation of the acetyl derivative of coenzyme A with oxalacetic acid to form citric acid. Acetyl coenzyme A or acetyl CoA, as shown in Figure 28, is the active acetate or active 2-carbon particle of the last decade. Most of the pantothenic acid of tissues can be accounted for by the presence of acetyl CoA. Acetyl CoA arises from the oxidation of fatty acids and from oxidative decarboxylation of pyruvic acid. These two major sources arise from fat and carbohydrate metabolism. Some amino acids, such as leucine, isoleu-

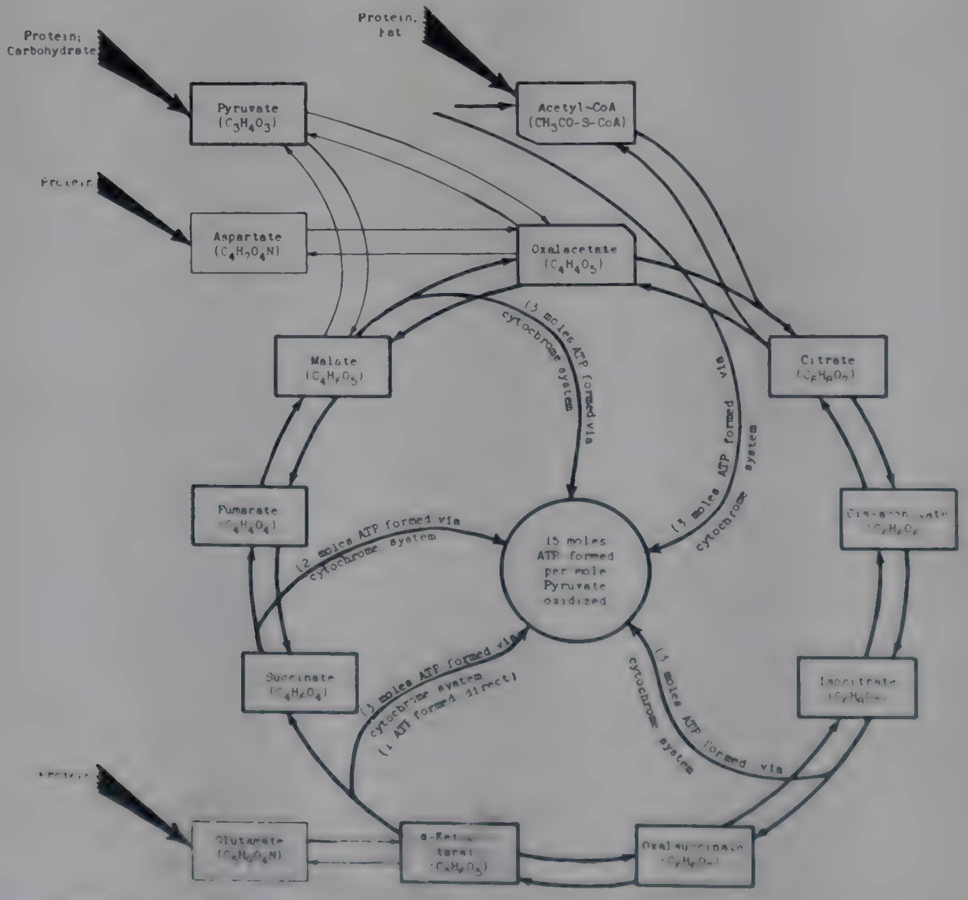

Protein; Carbohydrate
Protein, Fat
Pyruvate ($C_3H_4O_3$)
Acetyl~CoA ($CH_3CO-S-CoA$)
Protein
Aspartate ($C_4H_7O_4N$)
Oxalacetate ($C_4H_4O_5$)
Malate ($C_4H_6O_5$)
Citrate ($C_6H_8O_7$)
(3 moles ATP formed via cytochrome system
(3 moles ATP formed via cytochrome system
Fumarate ($C_4H_4O_4$)
Cis-aconitate ($C_6H_6O_6$)
(2 moles ATP formed via cytochrome system
15 moles ATP formed per mole Pyruvate oxidized
Succinate ($C_4H_6O_4$)
(3 moles ATP formed via cytochrome system (1 ATP formed direct)
(3 moles ATP formed via cytochrome system
Isocitrate ($C_6H_8O_7$)
Protein
Glutamate ($C_5H_9O_4N$)
α-Ketoglutarate ($C_5H_6O_5$)
Oxalsuccinate ($C_6H_6O_7$)

FIG. 27. The citric acid cycle. The diagram indicates sites where degradative products of carbohydrates, proteins and fats enter this metabolic cycle. In addition, the generation of ATP is indicated. (From E. C. Albritton, Standard Values in Nutrition and Metabolism, p. 189, Philadelphia, Saunders)

ine, phenylalanine and tyrosine, give rise to cetyl CoA, indicating the protein link to the citric acid cycle. Acetyl CoA is very active metabolically, in that it re-enters the various metabolic pools by virtue of its participation in reversible reactions which will be mentioned. It forms the acetoacetic acid made normally in small amounts by the liver and abnormally in large amounts in diabetes. In the main, however, it is the major fuel which feeds into the citric acid cycle. In man, the acetyl pool appears to be large and seems to be supplemented by excessive dietary consumption of fat. This pool feeds into fat and cholesterol synthesis and into the citric acid cycle. If the cycle cannot burn the excess acetate rapidly enough, it is conceivable that fatty acid and cholesterol synthesis would increase. In man, according to Keys,[18] excessive fat consumption leads to arteriosclerosis and its complications. It is conceivable that the liver is unable to burn acetate in the cycle fast enough to reduce the size of the acetate pool. With excess acetate available the liver probably synthesizes more cholesterol. In this sense, the liver, acetyl CoA and the citric acid cycle may be the determining factors in man's ultimate longevity. Those persons who synthesize less cholesterol presumably have less atherosclerosis.

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* The concentrations of citric acid cycle intermediates in the livers of fasted rats, expressed as milligrams per 100 Gm. of dry tissue according to Frohman et al.[13] are as follows: fumarate 33.4, α-ketoglutarate 11.0, oxalacetate 3.0, succinate 7.1, lactate 47.5, pyruvate 11.4, malate 5.9, cis-aconitate 0.4, isocitrate 1.8, citrate 8.9.

Acetyl CoA in the presence of the condensing enzyme reacts with oxalacetic acid to form citric acid. It is interesting to note that the methyl group is the active site of the condensation in this reaction as compared with the carboxyl group, which is active in the acetylation reactions. This indicates that acetyl CoA has an active "head" and an active "tail."

Citric acid is dehydrated and then hydrated to form cis-aconitic acid and isocitric acid by the enzyme aconitase. Isocitric acid is oxidized in the presence of isocitric dehydrogenase by TPN (ox) to form oxalosuccinic acid. The latter is oxidized to α-ketoglutaric acid in the presence of oxalosuccinic decarboxylase and manganese ions. The ketoglutaric acid is another key compound in the citric acid cycle. Amination with ammonia yields glutamic acid, or deamination of glutamic acid yields ketoglutaric acid, providing another link between protein, carbohydrate and fat metabolism. Ketoglutaric acid is decarboxylated to succinic acid.

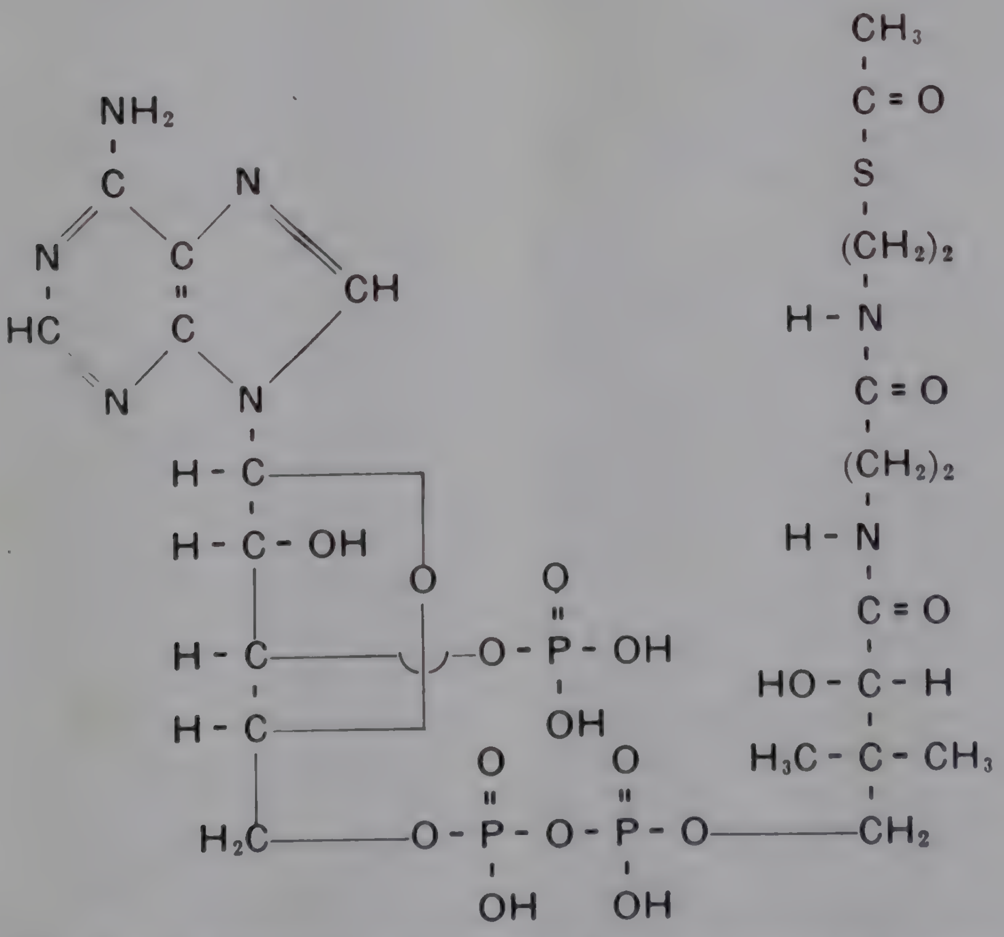


FIG. 28. The structural formula of acetyl coenzyme A. (From White et al.[42])

This oxidative decarboxylation is similar to that of the decarboxylation of pyruvic acid to acetyl CoA except that the high-energy compound succinyl CoA is produced. The factors lipoic acid and thiamine-pyrophosphate also participate in these reactions perhaps as a single compound lipothiamide-phosphate. The succinyl CoA can react with ADP and inorganic phosphate to yield succinic acid and ATP. This provides another important reaction for forming a high-energy bond. Succinyl CoA also can form succinyl derivatives of sulfonamides and probably reacts with glycine according to Shemin and Russell[33] to form the pyrrole rings of the porphyrins.

Succinic acid in the presence of succinic dehydrogenase is oxidized to fumaric acid, which then is hydrated to malic acid in the presence of fumarase.

Malic acid is oxidized in the presence of malic dehydrogenase to oxalacetic acid by DPN (ox), thereby completing the cycle. Malic acid can be oxidized and simultaneously decarboxylated to pyruvic acid, or pyruvic acid can be carboxylated and reduced simultaneously to malic acid. The reversal of this reaction is a major mechanism for the fixing of CO_2 by the liver. Oxalacetic acid and pyruvic acid can be aminated to their corresponding amino acids, aspartic acid and alanine, providing thereby further links with protein and carbohydrate metabolism.

When acetate is oxidized to CO_2 and water in the citric acid cycle, 12 high-energy-phosphate bonds are formed as ATP. ATP can store 10,000 calories per mole, which means that the oxidation of a mole of acetate leads to 120,000 calories stored in ATP. This amounts to approximately 60 per cent of the energy that acetate could yield if burned in a flame. The oxidation of one mole of glucose to 2 of pyruvate, which then are oxidized to acetyl CoA, which then enters the citric acid cycle to form CO_2 and water, yields 38 moles of ATP or 380,000 calories. This represents approximately 60 per cent of the energy available from glucose. A similar yield of ATP (that is approximately 60 % of the available energy) occurs when a fatty acid is degraded to acetyl CoA and then is oxidized in the citric acid cycle.

High-Energy Compounds

The oxidation of many substrates as indicated above occurs in a systematic, stepwise manner, yielding energy with each step. The rapid release of energy, as in a fire or in an explosion, would be disastrous in a biologic system. The energy of oxidation is incorporated into compounds which spark the biologically important reactions which of necessity in mammals occur in aqueous solutions at the constant temperature of 38° C. These compounds are ATP, creatine-phosphate, 1,3-diphosphoglyceric acid and phosphoenol pyruvate. These are the high-energy-phosphate esters abbreviated as ~P. When they are hydrolyzed they release a considerable amount of energy (from 8,000 to 16,000 calories per mole). These compounds participate in many of the phosphorylations noted above. They are involved in detoxication, synthesis of fats, carbohydrates and proteins, reabsorption of glucose in the renal tubule, synthesis of urea and so on. The energy released from oxidation when coupled with the build-up of high-energy phosphates is termed oxidative phosphorylation. Some examples have been given in the text to show how the synthesis of these high-energy phosphates is coupled with oxidation. Thyroxin, dinitrophenol, aureomycin and a few other compounds can uncouple oxidation from phosphorylation so that oxygen is used, but high-energy phosphates are not generated as rapidly.

In muscle, creatine-phosphate and ATP are generated. The creatine-phosphate acts as a reservoir of high-energy phosphate so that it can be used to form ATP for muscle contraction. In the liver the ATP generated by the citric acid cycle, in the main, participates in numerous reactions many of which are as yet poorly understood. We know how glucose can get to glycogen with the aid of ATP. However, we do not understand how it may play a role in providing energy for absorption and excretion in the liver as i undoubtedly does in the kidney. In the failing liver there are suggestions that this reservoi of high-energy phosphates has diminished For example, the glucose and galactose intolerance manifested after a test load ma be a reflection of too little available ATP although this fact might be explained other wise. The accumulation of blood ammonia and the development of hepatic coma may also be the result of an ATP deficiency.

The citric acid cycle in man, and particularly in the liver, is probably a most important metabolic system. The cycle probably has a metabolic deficit in liver disease, although adequate data are lacking to date. Its possible relationship to arteriosclerosis, as manifested by incomplete oxidation of acetate in this cycle in the liver, resulting in a larger acetate pool and hence a larger cholesterol pool, cannot be overemphasized. The associated functioning of this oxidative cycle with the oxidative chain, pyridine nucleotides to the cytochromes, accounts for the major oxidative activity of the liver. Perhaps 60 per cent of the energy so released is incorporated into high-energy bonds.

CHEMISTRY AND METABOLISM OF FAT

The liver normally contains from 3 to 5 per cent of its weight as fat except in disease states, where the fat may approach 50 per cent.

Lipid Metabolism

Bile acids of the liver promote emulsification and solubilization of fats so that the intestinal and the pancreatic hydrolytic enzymes become associated more intimately with these insoluble compounds and split them into fatty acids, glycerol, monoglycerides, diglycerides and triglycerides. These enter the lacteals and probably in the main (95%) are absorbed and pass into the thoracic duct and then into the peripheral blood. The absence of bile acids leads to, if not diminished hydrolysis, diminished absorption of fat. Vitamin K is not absorbed adequately in the absence of bile acids, which fact leads to a diminished synthesis of prothrombin in the liver and bleeding tendency. This type of prothrombin deficiency is treated readily with parenteral K. This forms the basis of a liver function test wherein prothrombin deficiency due to a lack of K can be distinguished from prothrombin deficiency due to parenchymal damage. In posthepatic obstruction, the absence of bile pigments along with the presence of unabsorbed, light-colored fats (caused by the concurrent absence of bile acids) causes the stool to be clay-colored. This fat is mainly calcium salts of fatty acids and sterols. Normally, other fatty substances are present in the stool because of incomplete absorption in the small intestine. Since fecal bacteria ferment these substances, they are generally nondescript. The bile acids in the intestinal tract are absorbed and enter the portal blood, where they are carried to the liver and later are excreted in the bile, thus making up the enterohepatic circulation. Bile acids in general enter the portal blood, whereas the fat enters the lymph. Butyric and soluble acids of lower molecular weight pass into portal blood to the liver, whereas larger fatty acids enter the lymph and later the thoracic duct.

Dietary cholesterol is partially absorbed from the intestinal tract. What remains is excreted in stool. The liver excretes cholesterol into the bile, which then enters the intestinal tract. Some is reabsorbed in the enterohepatic circulation, and some is excreted in the stool. Following ingestion of a fatty meal, the fat enters the lacteals, passes into the lymph, the thoracic duct and then into the peripheral blood to cause a temporary hyperlipemia. This fat consists of small globules, the chylomicra (mostly neutral fat) and a small increase of phospholipids. These are carried to the fat depots and the liver. Normally, the plasma is cleared of the excess fat from the meal. Some goes to the liver, and some to the depots. The plasma transports the depot fat to the liver for oxidation. The transport mechanism is related in some way to the phospholipids and the cholesterol esters. The depot fat provides energy when the body needs it. These depots are mobilized and replaced constantly and rapidly. In the rat the depot fat has a half life, by isotopic technics, of 8 days, as contrasted with that of liver fat which is 2 days. Aside from dietary fat there are other sources of fat for these depots (the carbohydrates and proteins) as will be shown later. The carbohydrates yield pyruvate, which makes acetyl CoA, which then may be resynthesized to fatty acids or cholesterol in the liver. The proteins yield amino acids, many of which ultimately yield small molecules and then form acetyl CoA and fatty acids. These fatty acids are characteristically the saturated ones which go to make the hard fat, while the dietary ones, particularly the vegetable oils, contain the unsaturated ones to supply the body needs for unsaturated fatty acids. The fatty acids move out of the liver as phospholipids and cholesterol esters.

Fatty-acid synthesis occurs in the liver. Many factors affect this synthesis such as:

1. Vitamin deficiencies (thiamine—necessary for pyruvate to form acetyl CoA; pyridoxine—necessary for participation in transamination to yield keto acids)
2. Starvation
3. Glycosuria, renal or phlorhizin
4. Diabetes

FATTY-ACID SYNTHESIS AND DEGRADATION

The synthesis and the oxidation of fatty acids have been described recently in a series of brilliant investigations by Lehninger, Lynen, Lardy, Green and many others. A fatty acid, for example butyric, $CH_3CH_2CH_2C{\diagup\!\!\!\diagup}^{O}$ ——OH, is converted to the butyryl CoA derivative in the liver, $CH_3CH_2CH_2C{\diagup\!\!\!\diagup}^{O}$ ——S CoA (—S CoA represents reduced coenzyme A in the sulfhydryl form). This compound condenses with acetyl CoA in the presence of the enzyme β-ketothiolase to form a 6-carbon compound, β-caproyl CoA, $CH_3CH_2CH_2C{\diagup\!\!\!\diagup}^{O}CH_2C{\diagup\!\!\!\diagup}^{O}$——S CoA. It in turn is reduced by DPN (red) in the presence of the enzyme β-ketodehydrogenase to the β-hydroxy acid, $CH_3CH_2CH_2\overset{OH}{C}H$-$CH_2C{\diagup\!\!\!\diagup}^{O}$——S CoA. The last loses a molecule of water in the presence of the enzyme crotonase to form an unsaturated derivative $CH_3CH_2CH_2CH = CHC{\diagup\!\!\!\diagup}^{O}$——S CoA.

This unsaturated acid is reduced by flavin adenine dinucleotide in the presence of acyl CoA dehydrogenase by the process of adding hydrogen to the double bond to form the saturated caproic acid CoA derivative, $CH_3CH_2CH_2CH_2CH_2C{\diagup\!\!\!\diagup}^{O}$——S CoA. This synthetic process can continue by the stepwise addition of acetyl CoA to form long chain fatty acids.

If the initial acyl CoA were acetyl CoA instead of butyryl CoA, the condensation product would be: acetoacetyl CoA, $CH_3C{\diagup\!\!\!\diagup}^{O}$-$CH_2C{\diagup\!\!\!\diagup}^{O}$—S CoA, and the reduced product would be β-hydroxybutyryl CoA, the unsaturated derivative crotonyl CoA and finally the saturated one butyryl CoA.

All these steps are reversible, which means that acetyl CoA derived from pyruvic acid can form any of the fatty acids (even numbers 4,6,8,—14,16,etc.) or that the larger molecular weight fatty acids can be broken down to acetyl CoA.

The acyl CoA derivatives can react with the hydroxyl groups of glycerol. In the process the fatty acid ester of glycerol (neutral fat) is formed, and coenzyme A is split off the fatty acid. Undoubtedly, cholesterol esters are synthesized in the liver in a similar manner from a fatty acid CoA derivative and cholesterol.

The oxidation of fatty acids proceeds to acetyl CoA, rather than intermediates mentioned above. If for some reason the acetyl CoA cannot enter the citric acid cycle and be metabolized further in the liver, it condenses with itself to form acetoacetyl CoA and on hydrolysis acetoacetic acid.

Reduction of acetoacetyl CoA by DPN (red) in the presence of the β-ketodehydrogenase produces β-hydroxybutyric acid. A small fraction of the acetoacetic acid is decarboxylated, probably spontaneously without intervention of an enzyme, to acetone. β-Hydroxybutyric acid, acetoacetic acid and acetone comprise the group of compounds known as the ketone bodies.

In diabetes the fatty acids in the liver are broken down rapidly to acetate in order to provide energy, since glucose is used inadequately. Synthesis in vitro of fatty acids from acetate, in the absence of insulin, is diminished. Presumably, this is true in vivo. This leads to a large pool of acetate. In diabetes the diminished glucose utilization is reflected ultimately in reduced activity of the citric acid cycle. It is here that acetate condenses with oxalacetate to form citrate, and so on. In this event with reduced use of acetate for fat synthesis and reduced use in the citric acid cycle, acetate accumulates. In the process it condenses with itself to form acetoacetyl CoA. When deacylated in the liver it forms acetoacetic acid. Blood flowing from the liver carries it to the other tissues where

: can be acylated again and thrust back into he metabolic pool to be utilized further. The ver does not have the proper acylating enyme, so that acetoacetic acid accumulates n the liver. When the production in liver is igh, as in situations cited below, the output xceeds the ability of peripheral tissues to ise the ketone bodies. In this event the acids ccumulate and cause a metabolic acidosis, vhich in this special case is called ketosis. The blood ketone bodies are high, and these apidly appear in the urine. In starvation, a imilar phenomenon occurs in that the fatty cids break down to acetate but are not utiized rapidly by the citric acid cycle. In hlorhizin diabetes or renal glycosuria the oss of glucose presumably is reflected in liminished activity of the citric acid cycle in he liver and accumulation of acetate with he resultant excess formation of ketone odies. A similar situation is achieved by eeding a low-carbohydrate, high-fat diet which leads to ketosis. In Von Gierke's disease where glycogen is not mobilized adequately and where hypoglycemia occurs, ketosis, hyperlipemia and hypercholesterolemia develop. The above suggestions explaining ketosis appear to apply in this disease.

The author has seen an acute fatal hepatitis where a severe acidosis occurred. It may be that this acidosis reflects a failure of the citric acid cycle with accumulation of ketone bodies as a result. Rechnagel and Potter[27] in in vitro experiments have shown that inhibition of the citric acid cycle in the liver leads to a greater synthesis of ketone bodies.

The body may attempt to overcome the high acetate production by the liver by condensing it with another acetate molecule to form acetoacetic acid. Since the acetoacetic acid is used better in peripheral tissues than in liver, because of the inability of the liver to put it back into the metabolic pool, this may be a protective device or trapping system for acetate. If the acetate accumulates, the liver converts it into cholesterol, which it then can excrete via the bile. This, too, may be considered a defensive mechanism. Unfortunately, the cholesterol is not excreted rapidly enough in man, so that it accumulates in his arteries with ultimate serious consequences. If it does get excreted rapidly, it

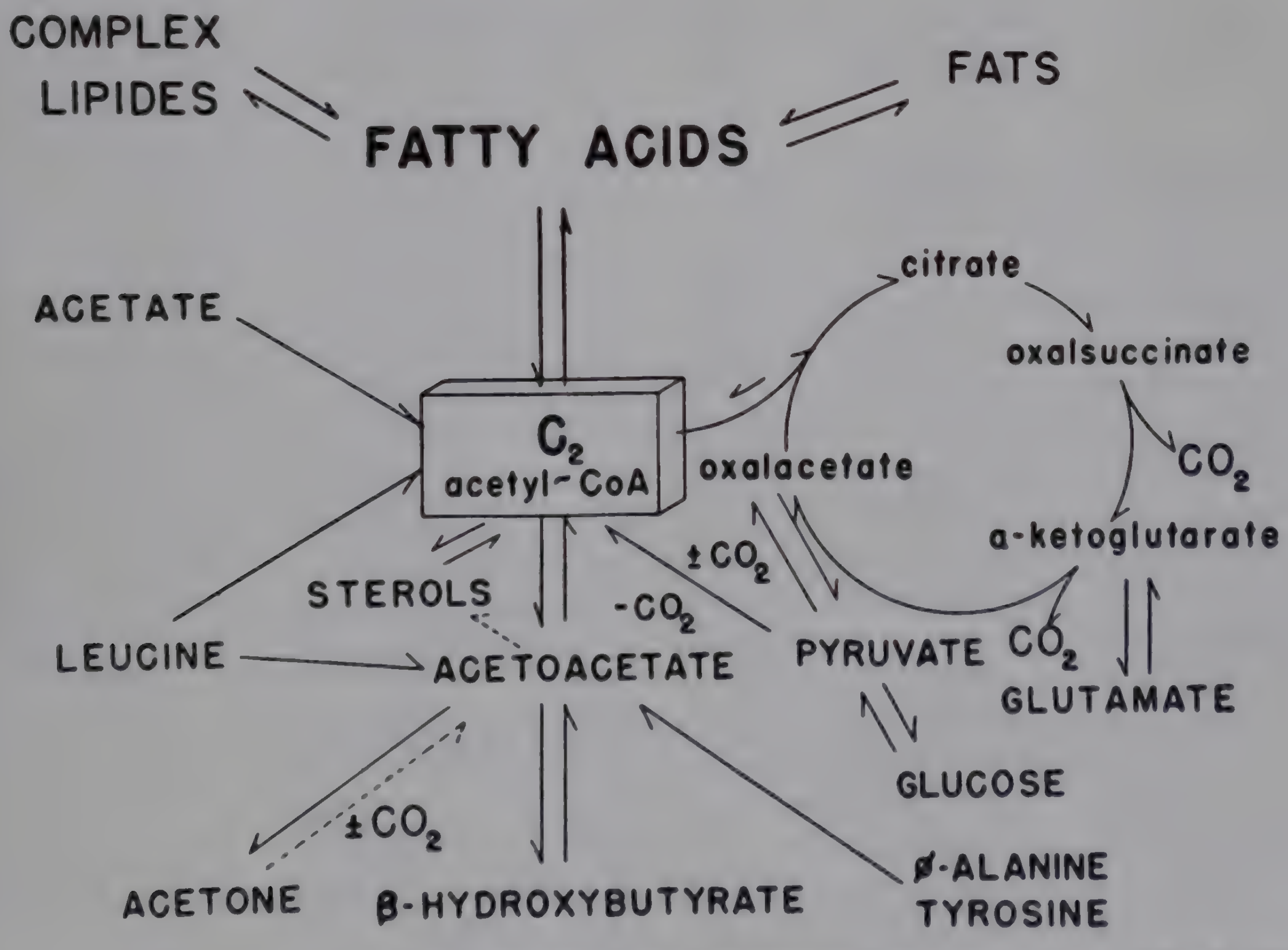


FIG. 29. The central role of acetyl CoA in intermediary metabolism. (Chaikoff, I. L., and Brown, G. W., Jr., in D. Greenberg, Chemical Pathways of Metabolism, vol. 1, p. 301, New York, Acad. Press)

may form gallstones. Keys[18] has shown in numerous population studies that men on high-carbohydrate, low-fat diets have statistically lower blood cholesterol levels and longer life spans than those who consume less carbohydrate and more fat. The role of the liver in longevity has been underestimated in this regard.

The diagram in Figure 29 suggests the numerous pathways that acetyl CoA takes and the numerous compounds which contribute to this metabolic pool.

It can be seen from this diagram that fat can go to acetyl CoA, which then enters the citric acid cycle to become citrate. Ultimately, oxalacetate is formed, which can yield pyruvate by decarboxylation. Thus the pyruvate can enter the glycolytic system and be synthesized to glucose. This has been shown with isotopically labeled substances and ends an old academic question of whether or not fat is converted to carbohydrate. The answer heretofore was always in doubt because of the quantitatively small contribution of fat to carbohydrates. The reverse has been anticipated and known for years, viz., that carbohydrate readily goes to fat. The diagram also demonstrates how constituents of protein can form acetyl CoA and fat or vice versa.

FAT TRANSPORT, FATTY LIVER AND THE LABILE METHYL

Since the liver is the major site of fatty-acid oxidation, the depot fat must be transported to the liver, where it is broken down to acetate or ketone bodies. The depot fat consisting of neutral fat is mobilized by some unknown mechanism that can be stimulated by the pituitary. Injection of a pituitary factor can lead to rapid fat mobilization, hyperlipemia and fatty liver because the liver cannot oxidize it fast enough. The rapid mobilization of fat and transport to the liver can lead to rapid deposition of fat in the liver. This occurs in poisoning by carbon tetrachloride or white phosphorus, in starvation, diabetes and after pituitary administration. The excessive transport of fat to the liver is one mechanism for the development of fatty liver.

A supply of labile methyl groups is needed for the synthesis of choline and phospholipids by the liver. The choline type of phospholipid in some manner can solubilize and carry fat away from the liver. If the lecithin type of phospholipid diminishes, the ability to carry fat away from the liver diminishes and fat accumulates. This appears to be the cause of the labile-methyl-deficiency fatty liver. Compounds that provide methyl groups for choline synthesis are methionine and betaine. The body appears to be capable of synthesizing a small fraction of its methyl group need (perhaps 10%). This methyl group has been called labile methyl (du Vigneaud[10]) and by the process of transmethylation can convert ethanolamine to choline.

Cantoni[6] has shown that the methyl is transported by S-adenylmethionine, which he calls "active methionine." The major methyl donor appears to be methionine, hence the success of high protein diets in moving fat out of the liver (lipotropic) because they provide methyl groups for choline synthesis. Compounds that consume methyl groups in the liver are antilipotropic. Nicotinamide is such a compound because it is methylated in the liver to form N-methylnicotinamide. Guanidoacetic acid is another, because it consumes a methyl group in its conversion to creatine. Unfortunately, the lipotropic effect of choline is demonstrated only in true choline deficiency. Some fatty livers develop in man which are unexplained and persist, regardless of therapy. The relationship of inositol, biotin, cholesterol and lipocaic to the development or mobilization of fat in the liver is unsettled.

Just as there is a 2-carbon pool, now represented by acetyl CoA, so there is a 1-carbon pool. It appears that this pool represents some derivative of the formyl group. This presumed derivative can be reduced in vivo to yield the labile methyl group (to a limited extent). Donors of this 1-carbon fragment are glycine, serine, choline, betaine and methionine. Vitamin B_{12} and folic acid derivatives are related in some way to this pool in that deficiencies of these vitamins are manifested by inefficient use of the labile methyl group.

PHOSPHOLIPIDS

The important property of these compounds is their simultaneous fat and water solubility because of the polar and the nonpolar chemical groups. Thus they can facilitate solution or emulsion of fats. Because of this property it has been suggested that phospholipids transport fat.

The supposition that phospholipids carry fatty acids has been challenged by the data of Bloom et al.,[4] which showed that 96 per cent of labeled palmitic acid absorbed into the lymph was in the nonphospholipid form. Phospholipid synthesis in the liver is great. Lecithin turnover in the animal liver occurs in 1 day. Its synthesis is limited by the supply of dietary methionine or choline. The complete synthesis of plasma phospholipids occurs mainly in the liver from the various components (choline, phosphate, fatty acids of 16 to 18 carbons, and glycerol).

STEROLS AND BILE ACIDS

Cholesterol is the most abundant sterol of the animal. It is synthesized from acetyl CoA by as yet undefined enzymatic reactions. Although it can be made in the kidney and the adrenal as well as in other tissues, the major source is the liver. In addition to synthesizing cholesterol, the liver also excretes it into the bile and the intestinal tract. Occasionally, the high content of cholesterol in bile and its supersaturation is accompanied by cholesterol deposition in the gallbladder and by stone formation, leading to obstruction of the biliary tree. The cholesterol gets into the blood where it maintains a relatively constant value for any single individual. Undoubtedly the cholesterol ester fraction is synthesized in the liver but is also formed in slight amounts in the intestinal wall. It too maintains a constant value for any one individual. In liver disease the serum cholesterol-ester fraction may diminish, probably reflecting reduced liver synthesis. The mechanism is explained inadequately. A rise of serum cholesterol appears to be accompanied by a rise of phospholipids, except in the presence of liver disease. The level of free cholesterol in serum correlates with the total phospholipids. This mechanism, presumably, is controlled also in the liver.

A mechanism for the synthesis of cholesterol is outlined in the diagram below.

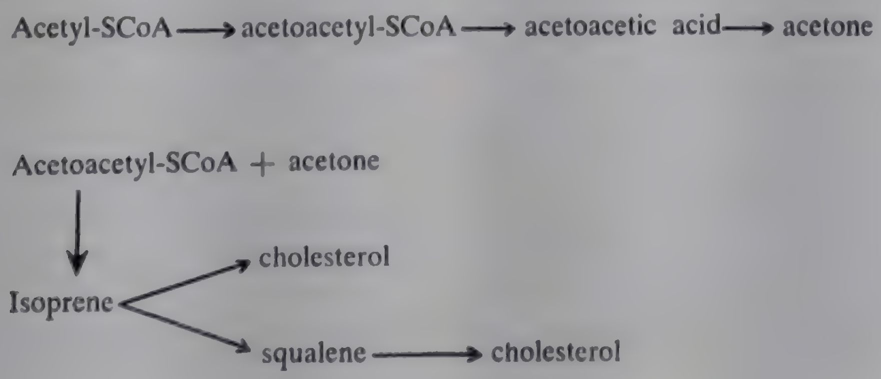
There is good evidence to show that the supply of cholesterol entering the liver controls the synthesis by the liver. A high intake reduces liver synthesis, while a low intake favors liver synthesis. This may be one reason why a diet low in cholesterol does not reduce serum cholesterol.

With severe parenchymal liver damage plasma cholesterol falls, and the relative amount of cholesterol ester falls. Since the synthesis of these compounds requires energy (ATP and HSCoA) it may well be that a failing liver cannot provide this energy.

The liver metabolizes the steroid hormones related to cholesterol, e.g., estrogens, testosterone, the corticoids and progesterone. In liver failure the ability to metabolize these diminishes; hence, the free or unconjugated urinary steroids may be increased in liver disease, although the total excretion (free and combined) may be decreased.

The bile acids are synthesized in the liver from cholesterol. In man 4 acids have been isolated. Cholic acid occurs in largest amount and most of it is conjugated in the liver with the amino acids taurine or glycine to form taurocholic ($RCO\text{-}NHCH_2CH_2SO_3H$) and glycocholic ($RCO\text{-}NHCH_2COOH$) acids.

These acids are considerably stronger than the fatty acids and readily form anions (or salts) at the pH of body fluids. Their peculiar structure allows them to be water soluble and fat soluble like the phospholipids. Thus


Acetyl-SCoA → acetoacetyl-SCoA → acetoacetic acid → acetone
Acetoacetyl-SCoA + acetone
Isoprene
cholesterol
squalene → cholesterol

they are able to participate in intestinal digestion by facilitating solution or emulsion of fat. The liver readily removes the bile acids from peripheral blood and excretes them into the bile. The secretory mechanism for these compounds, as for bilirubin and bromsulfalein, remains a mystery.

Starvation and straight carbohydrate diets decrease bile acid secretion, and presumably synthesis, while high protein diets increase it. The bile acids are reabsorbed from the intestine and recirculate in the enterohepatic circulation. The conservation of bile acids by this mechanism is not complete; a small fraction is lost in the intestinal tract by fermentation, and some appears in the feces.

As would be expected, parenchymal injury reduces the excretory rate of bile acids, while obstruction leads to an accumulation in the blood. If bile acids were formed in other tissues besides the liver as is bilirubin, the rise in complete biliary obstruction would be continuous, which fortunately it is not. This suggests a mass action effect on the synthesis of bile acids when a sufficiently high concentration is present, as is the case with cholesterol.

In the clinical study of liver disease the variations of serum fats are a reflection of (1) the kind of disease, (2) the state of the patient at the time of study, (3) the degree of biliary obstruction, (4) the nature and the severity of the parenchymal damage, (5) the state of the body fat depots and the extent to which they are being mobilized. Some of these variations will be discussed in other sections. An elevation of serum fat associated with lowered serum albumin and elevated serum globulins may lead to an elevation of the thymol turbidity test and vice versa.

PROTEIN AND AMINO ACID METABOLISM

Peptide Bonds

The proteins represent an amazing group of large molecular weight compounds, easily synthesized in biologic systems from amino acids. The constant breakdown in the body is equaled by the constant synthesis, with molecules of the diet entering into the synthesis and the degradation, while the protein molecules of the body are being degraded. In addition, the other metabolic systems (carbohydrate, fat, citric acid cycle, urea) are tied intimately with the synthesis and the breakdown of body proteins.

The liver plays a most important role in the synthesis of the special proteins, such as those required in the blood-clotting mechanism (fibrin, prothrombin), the plasma proteins (albumin and perhaps 80% of the globulins), and the liver enzymes. Defects in synthesis are manifested by bleeding, abnormal liver function tests, hypoalbuminemia and reduced enzyme activity of the liver. Synthesis of proteins in general is a major unsolved biologic process. Some evidence has been presented to indicate that amino acids are incorporated directly into proteins, and other evidence has indicated that amino acids are incorporated into peptides, which then are synthesized into proteins.

The peptide bond of proteins is that which links two amino acids together. The peptide link appears to be made through condensation of a CoA derivative of one amino acid with another. ATP and an enzyme appear to be required for the synthesis. It is essential in peptide bond or protein synthesis to have an available reservoir of high-energy phosphates. The effect of insulin on muscle to increase amino acid utilization may be mediated through its stimulation of muscle to use more carbohydrate, which ultimately builds ATP and hence allows more peptide synthesis. It has been shown experimentally that carbohydrate favors the optimum utilization of amino acids for protein formation and in addition spares the body protein by preventing its being used for its caloric content. Carbohydrate favors amino acid utilization when it is administered simultaneously with amino acids rather than at different times. This also suggests the above relationship in which carbohydrate provides the energy required for the synthesis of protein from amino acids. How this mechanism works in the liver is poorly understood. The synthesis of the peptide bond of hippuric acid in the liver from benzoic acid and glycine is essentially like the synthesis of a peptide. Benzoyl CoA is formed which reacts with glycine to form hippuric acid. This synthesis appears to be diminished in liver disease and in starvation, which may mean that in these two conditions the reservoir of high-energy phosphates is depleted. Other acylations, such as the benzoylation of glycine, are performed in the liver. For example, it is here that acetylation of the sulfonamides, *p*-aminobenzoic acid and tryptophane occur to form the corresponding acetyl derivatives.

All of these reactions, peptide-bond and acyl-derivative synthesis, are energy-requiring reactions, dependent upon the high-energy compounds.

PLASMA PROTEINS AND LIVER FUNCTION TESTS

In starvation the serum albumin usually falls, while the globulin remains essentially constant. This might possibly be interpreted as reduced synthesis of albumin in the liver because of a reduced high-energy-phosphate pool. The latter would result from a decreased supply of carbohydrate as in starvation. In liver disease of the inflammatory type, for example cirrhosis, the total serum proteins may be normal, the albumin low, and the globulins high. The globulin elevation appears to be the result of the inflammation. The nature of this synthesis is obscure; however, if globulins are synthesized, high-energy phosphates undoubtedly are used. If the ATP supply is limited, it might be expected that the globulins are synthesized in the liver at the expense of the albumin. Furthermore, the diseased liver may not have the capacity to supply its normal demands for ATP. Suggestion of a reduced ATP reservoir is indicated by the decreased tolerance for glucose and galactose and the decreased synthesis of hippuric acid. In this regard what is needed for evaluating liver function is a test for measuring the ATP content or ATP regenerative capacity of the liver.

The liver function tests, such as the cephalin cholesterol flocculation, zinc turbidity, lipid turbidity, ammonium sulfate turbidity and others, are practically all measures of the simultaneous lowering of serum albumin, the rise of globulins, and the change in serum lipids, rather than the production of new and unusual proteins by the diseased liver. The main abnormalities in these tests occur in acute viral hepatitis where albumin is generally lower than normal, globulins are above normal, and the serum fat is above normal. In some cases of severe parenchymal damage associated with cirrhosis these tests may remain within normal limits. This particularly may occur where the serum globulin and the lipids are not very high. The empiricism involved in these protein tests does not detract from their great value in studying and following the clinical course of liver disease.

PROTEIN RESERVOIR IN THE LIVER

Proteins make up 75 per cent of the dry liver. Aside from the structural components much of these proteins are the liver enzymes, or are associated in some way with enzymatic action, or are precursors of enzymes. In wasting or starvation the liver size, the protein content and the enzyme content diminish, indeed more rapidly than in other organs except perhaps for the intestinal tract. The liver of rats as shown by Addis[1] lost 20 per cent of its protein in a 2-day fast and as much as 40 per cent in longer periods. This suggests that the liver provides a labile supply of protein which might be called a store or a reserve. Also, it has been shown in experimental animals that the protein content of the liver varies with protein intake. Harrison[15] has found that the decrease of liver size in starved rats is the result of loss of cytoplasmic constituents from the liver cells. Almost all of the glycogen disappeared in the first 24 hours. The cells lost protein throughout the 4-day fast, and more loss occurred in the cells of female than male rats. A loss of cytoplasmic water, phospholipids and ribose nucleic acid also occurred. The male liver cells appeared to lose their small store of fat and then gain a small store of glycogen after the initial loss (1 day), whereas the female cells increased their store of fat (up to 7%) during the fast but lost more of their glycogen. Wainio et al.,[39] in their study of oxidative enzymes in the livers of protein-depleted rats, found that all of 8 enzymes measured (cytochrome oxidase, succinoxidase, succinic dehydrogenase, D-amino acid oxidase, DPN-cytochrome c reductase, uricase, xanthine oxidase and pyruvic acid oxidative enzymes) were decreased in amount, and that the total liver size and liver protein were also decreased as compared with livers of adequately fed rats. Xanthine oxidase, an enzyme which is associated with the oxidation of many substrates, was lost more rapidly than the liver protein.

The stress of inflammation increases protein loss from the liver. The effect of a sterile turpentine abscess[44] on turnover of serum albumin and fibrinogen is great. The normal biologic half life of albumin in the dog is 9 days, whereas following the turpentine abscess the half life is 1.5 to 2 days. The fibrinogen is also turned over rapidly during the stress of inflammation. The globulin fraction, however, is not affected and turns over at its usual rate. This effect of inflammation to increase the rate of albumin breakdown may be another contributory factor to the decreased serum albumin found in inflammatory diseases in general, and of the liver in particular.

The enzyme loss may be an adverse effect as shown by the greater susceptibility to injury of protein-depleted livers to chloroform and other hepatotoxic agents. Liver function is impaired in many clinical diseases where protein depletion occurs, such as ulcerative colitis, tuberculosis and gastro-intestinal cancer.

The protein part of the enzyme seems to act as an electron reservoir with the coenzyme acting as the valve. In addition, the protein modifies the redox potential or activity of the coenzyme as indicated above for the flavoprotein enzyme. Thus, the diminution of liver enzymes and liver protein may have an adverse effect on the oxidative activity of the liver in vivo.

Protein degradation in the liver initially is a hydrolytic process in which peptide bonds are split by the hydrolytic enzymes to amino acids. The amino acids enter the body pool which, in man, has been estimated as 2.2 Gm. of amino nitrogen.[28] The whole body pool of nitrogen is great, but the actual rapidly turning-over protein is in the liver, the plasma and the viscera, which amounts to approximately 140 Gm. of nitrogen or about 1 Kg. of protein. This represents about 10 per cent of the total body nitrogen. The turnover of this active protein pool in man, which occurs to a large extent in the liver, is 2.5 days. The implication is that reduction of this active protein pool in many disease states associated with negative nitrogen balance may have an adverse effect on the liver and its metabolic functions.

The extracellular water contains about 40 per cent of the free amino acids; the remainder appears to be in the tissues. That coming to the liver via the portal blood (very little enters via the lymph) is removed almost completely by the liver. The concentration of plasma amino acids in this way remains relatively constant in spite of frequent dietary supplies of amino acids equivalent to 100 times the circulating amino acids. Although other tissues can metabolize amino acids, the metabolic activity of the liver and its position in the digestive system make it the major site of amino acid metabolism. The amino acids are not only degraded here but also enter into the liver structure rapidly while the proteins already there are breaking down. In man the half life of the liver proteins has been estimated as 2.5 to 10 days, as compared with muscle with a half life of 150 days.

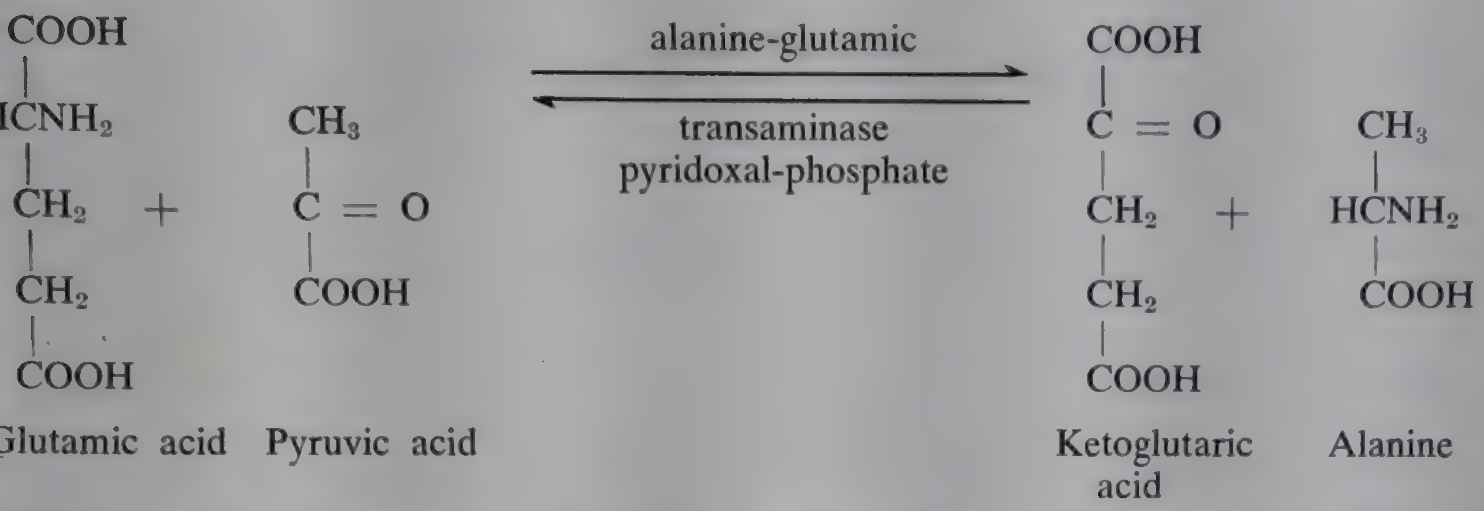
Growth hormone, insulin and testosterone have an effect on protein synthesis in that they favor anabolism rather than catabolism, whereas 17-hydroxycorticosterone favors gluconeogenesis and breakdown of proteins. Undoubtedly, the action of endocrines on the liver is important.

The liver synthesizes most of the plasma proteins which are turning over rapidly. In the rat it actually may synthesize a quarter of the total circulating plasma proteins in a day.

OXIDATIVE DEAMINATION AND TRANSAMINATION

The degradation of amino acids occurs mainly in the liver. One method is by oxidative deamination, resulting in the formation of a keto acid and ammonia. The reaction is catalyzed by the enzyme L-amino acid oxidase, a flavoprotein. Thirteen monoamino, monocarboxylic acids can be so oxidized. Glycine oxidation is catalyzed by glycine oxidase; glutamic acid oxidation in the liver is aided by the special enzyme glutamic dehydrogenase. The latter enzyme is present in the liver in large amounts, whereas the amino acid oxidase is present in lesser amounts.

Transamination, the process in which the



mino group of an amino acid is transferred o a ketoacid, is a far more important mech-nism for initiating amino acid oxidation. The reversal of this reaction may be the final tep in the synthesis of an amino acid. The xchange probably takes place for a large umber of amino acids and perhaps for all. An example of the transamination reaction o form alanine is shown above.

This reaction is catalyzed by the enzyme lanine-glutamic transaminase. The coenzyme is a pyridoxine derivative and phosphate ester.

Transamination in the liver appears always to involve glutamic acid and glutamic acid dehydrogenase, which points to its key role here. The amino group is removed from glutamic acid in the presence of this enzyme, which then provides α-ketoglutaric acid as an acceptor for another amino group. The keto acids pyruvic, oxalacetic and ketoglutaric are all involved in carbohydrate metabolism and the citric acid cycle. By transamination they enter the protein pool as amino acids.

Metabolism of Some Amino Acids

A number of specialized degradative and synthetic reactions of the amino acids are known in detail. Only a few reactions can be mentioned here.

Glycine, the simplest amino acid, is oxidized to glyoxylic acid in the presence of glycine oxidase, a flavoprotein found in the cytoplasm of liver cells. The glyoxylic acid residue has been found in glucose and other metabolic pools. Glycine reacts in some way with an active 1-carbon particle to form serine. Serine may go reversibly to glycine. In addition, glycine can contribute to the active 1-carbon or "formyl"-carbon pool. Glycine is also linked to cholic acid in the liver to form the bile acid glycocholic acid. It is linked similarly to benzoic acid to form hippuric acid. Glycine in the liver contributes its carbon chain to make creatine. The amidine group of arginine is transferred to glycine to make guanidoacetic acid, which is methylated in the liver by active methionine to form creatine.

Glycine contributes to the structure of uric acid and to the structure of glutathione. The incorporation of labeled glycine into liver glutathione appears to occur faster than into liver proteins. Glycine participates in the synthesis of pyrrole rings. As discovered by Shemin and Russell,[33] glycine condenses with active succinate, probably succinyl CoA, to form amino-β-ketoadipic acid. The latter is decarboxylated to form aminolevulinic acid, which can condense with itself to form porphobilinogen and ultimately porphyrins (Fig. 30). A biochemical disturbance resulting in the accumulation of porphobilinogen occurs in acute intermittent porphyria and according to Watson[40] involves the liver, hence his term "porphyria hepatica."

Alanine is synthesized readily from pyruvic and glutamic acids by transamination or is degraded in this manner. Conversion of alanine to pyruvic acid, which in turn goes to glucose, explains its glucogenic effect.

Cysteine, cystine and methionine, the sulfur-containing amino acids are closely related. Methionine in the liver can yield its sulfur to serine to form cysteine, and the latter on oxidation yields the disulfide cystine.

As might be expected, the 3-carbon chain of cysteine can form glucose. Oxidation of its terminal SH group to a sulfonic acid group yields cysteic acid, which on decarboxylation yields taurine. The latter combines with cholic acid to form taurocholic acid.

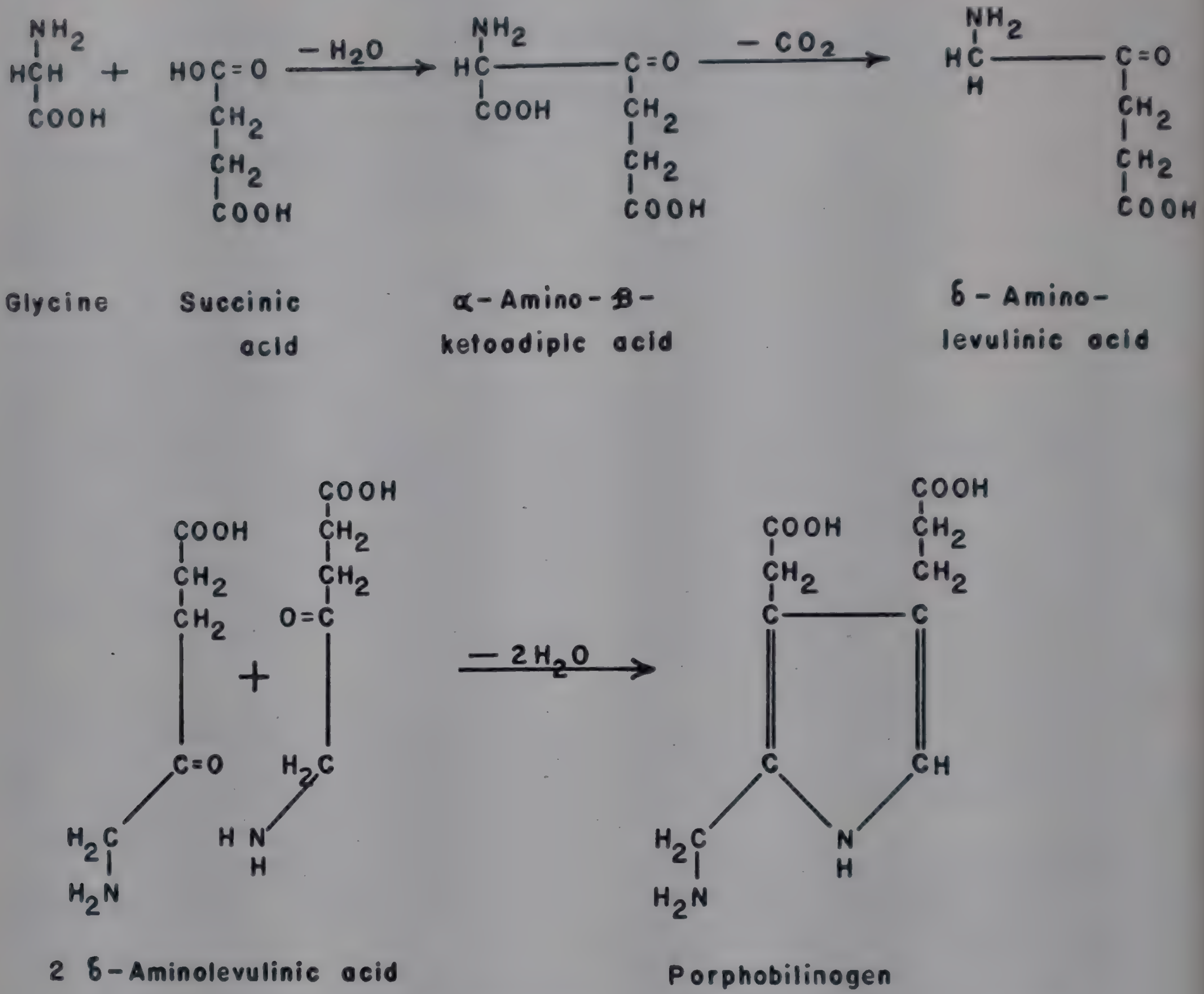


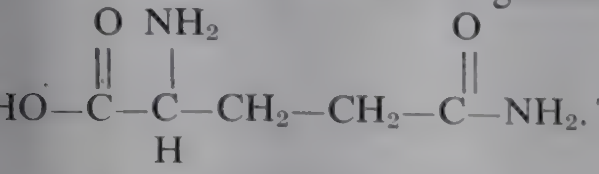
FIG. 30. The synthesis of porphobilinogen from glycine and succinic acid.

The methionine as indicated above provides its methyl group for the labile methyl pool. Choline is synthesized with these methyl groups to provide choline for phospholipid synthesis. It is because of this that the sulfur amino acids have received so much study in liver disease. In experimental animals and in man, particularly the poorly fed alcoholic, the labile-methyl deficiency is manifested by fat deposition in the liver. Methionine administration in this event facilitates removal of the fat. Diets containing methionine in the proteins also have the same effect, and high-protein diets are more effective than low-protein diets. There seems to be no justification to apply this rational treatment of the fatty liver due to the labile-methyl deficiency to other liver diseases. As a matter of fact, high-protein diets may be detrimental. Cystine has been shown to increase fat deposition in young rats on a protein and labile-methyl deficient diet. This effect appears to be the result of stimulation of growth which makes the choline deficiency worse. Therefore, cystine is not a toxic amino acid if viewed in this sense. In choline and cystine deficiency, the cystine deficiency contributes to liver necrosis, which ultimately leads to fibrosis. In the presence of some methionine, fatty liver, not necrosis, will occur. Ethionine is the ethyl thio ether of homocysteine analogous to methionine, the methyl ether of homocysteine. Animals that have been fed ethionine fail quickly because of the incorporation of this unnatural compound into proteins and other sites where methionine is active.

Proline and Related Acids. The metabosm of the amino acids glutamic, ornithine, roline and hydroxyproline are closely reated, as shown by isotopic studies.

These compounds can form ketoglutarate nd ultimately glucose.

Glutamine is the amide of glutamic acid,



$$HO-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{NH_2}{\overset{|}{C}}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-NH_2$$

The energy for the synthesis from ammonia and lutamic acid comes from ATP. Two hepatic nzymes catalyze its deamidation. The deamidation appears to occur in the process of ransamination as described by Meister.[21] He howed that 28 amino acids could be synthesized by the glutamine transamination from heir corresponding α-keto acids. This system nay be more important in the kidney than n the liver. Aspartic acid, asparagine and xalacetic acid form a similar group of compounds which participate in deamidation and ransamination.

The relationship of ammonia and glutamine to hepatic coma will be mentioned below.

Phenylalanine, Tyrosine and the Phenylurias. Phenylalanine is an essential amino acid which is oxidized in the liver to tyrosine. The enzyme involved is phenylalaninase. Either of these amino acids can undergo transamination to yield the corresponding keto acids phenylpyruvic and *p*-hydroxyphenylpyruvic acids. Reduction of the keto acids yields the corresponding hydroxy acids, phenyllactic and *p*-hydroxyphenyllactic acids. Oxidation of *p*-hydroxyphenylpyruvic acid is facilitated by the liver enzymes in the presence of vitamin C and folic acid to yield homogentisic acid. This last compound is oxidized further in the presence of the enzyme homogentisase (which is found in the liver) to fumarylacetoacetic acid. The latter compound is split to fumaric and acetoacetic acids in the presence of fumarylacetoacetase. These two end products enter the metabolic pools.

Patients with phenylpyruvic oligophrenia manifest inadequate activity of liver phenylalaninase and cannot hydroxylate phenylalanine to tyrosine. Phenylalanine accumulates, and the kidney and the liver deaminate it to phenylpyruvic acid, which is excreted in the urine. Since phenylpyruvic acid is decarboxylated readily to phenylacetic acid and is also reduced easily to phenyllactic acid, these appear in the urine also but to a lesser extent. The appearance of these 3 acids in urine has led to the term phenyluria. The occurrence of mental deficiency with phenyluria and deficiency of the enzyme phenylalaninase are acknowledged; however, the mechanism of the brain defect is obscure.

In hydroxyphenyluria the oxidation of tyrosine is diminished, and it accumulates in the blood. The kidneys and the liver deaminate tyrosine which is decarboxylated later or reduced with the resultant urinary excretion of *p*-hydroxyphenylpyruvic, *p*-hydroxyphenylacetic and *p*-hydroxyphenyllactic acids. Hydroxyphenyluria has been observed in ascorbic acid deficiency, pernicious anemia, premature infants and a case of myasthenia gravis.

When the liver enzyme homogentisase is absent, homogentisic acid is not oxidized further. It accumulates in the blood and is excreted in the urine. Homogentisicaciduria occurs in the hereditary disease alcaptonuria and also may occur in ascorbic acid deficiency.

The ultimate metabolism of phenylalanine is affected by the absence of one of the related enzymes of the liver. The accumulation of some of the products of metabolism in the blood leads to their further metabolism or excretion by the kidney. The appearance of these components in the urine suggests a biochemical defect of the liver. These reactions are summarized in Figure 31.

Tryptophane is another essential amino acid. Its absence is followed immediately by negative nitrogen balance and rapid deterioration of the animal. Tryptophane is oxidized in the liver with several products resulting, of which some are kynurenine, kynurenic acid, xanthurenic acid and nicotinic acid.

In pyridoxine deficiency kynurenic acid formation appears to be retarded, while xanthurenic acid formation and excretion in the urine are increased. Nicotinic acid deficiency is relieved by adding tryptophane and worsened by removing tryptophane from the diet. The bacterial flora of the intestinal

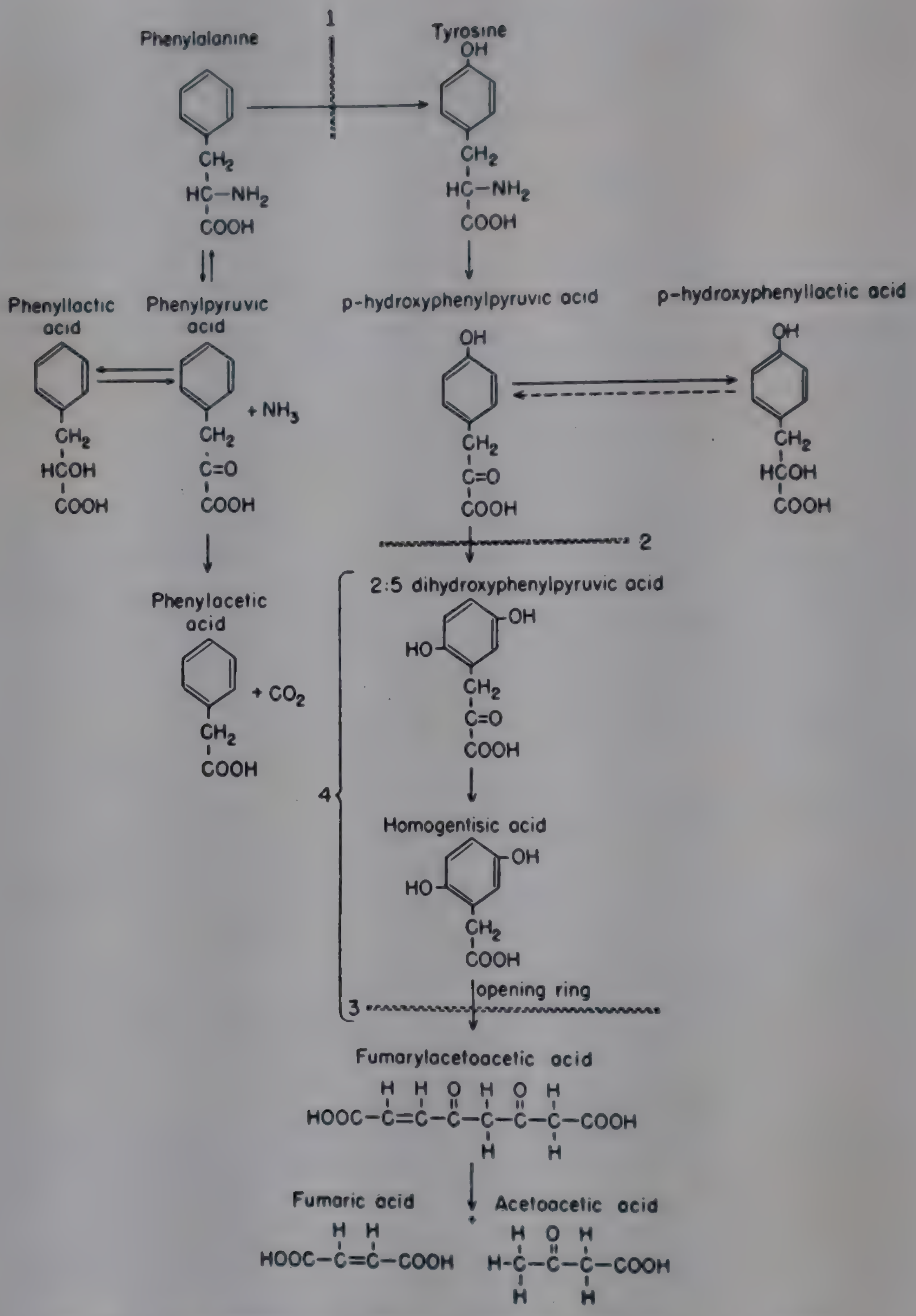

1
Phenylalanine
Tyrosine
OH
CH2
HC–NH2
COOH
Phenyllactic acid
Phenylpyruvic acid
p-hydroxyphenylpyruvic acid
p-hydroxyphenyllactic acid
HCOH
C=O
+ NH3
2
2:5 dihydroxyphenylpyruvic acid
HO
Phenylacetic acid
+ CO2
4
Homogentisic acid
opening ring
3
Fumarylacetoacetic acid
HOOC–C=C–C–C–C–C–COOH
Fumaric acid
HOOC–C=C–COOH
Acetoacetic acid
H–C–C–C–COOH

FIG. 31. The metabolic pathways of phenylalanine. A deficiency of phenylalaninase at Site 1 causes phenylpyruvic oligophrenia. An enzyme or ascorbic acid deficiency at Site 2 leads to the increased excretion of *p*-hydroxyphenylpyruvic acid as found in tyrosinosis, ascorbic acid deficiency and premature infants. A deficiency of homogentisase at Site 3 leads to accumulation of homogentisic acid and excretion in the urine which is the case in alcaptonuria. The failure of a group of degradative reactions involved at Site 4 occurs in ascorbic acid deficiency and results in the appearance of *p*-hydroxyphenylpyruvic and homogentisic acids in urine. (From Greenberg, in D. M. Greenberg: Chemical Pathways of Metabolism, vol. 2, p. 81, New York, Acad. Press)

act metabolize tryptophane to indole and katole which, when absorbed, must be etabolized by the liver. In this case these ompounds are detoxified by conversion to lfate esters and then are excreted in the rine. Also, tryptamine may arise in the owel from tryptophane. The aberrations of ese metabolic processes in liver disease, if resent, are obscure.

Urea Synthesis

A group of amino acids (ornithine, citrul- ne, arginine and aspartic acid) are involved irectly in urea synthesis. The ammonia reulting from the deamination of amino acids ust be removed rapidly to avoid the toxicity f the ammonium ions. The liver is the major nd probably only site of urea formation. Its bility in this regard is very great. Urea synthesis may be one of the last functions of the liver to disappear. Historically, this synthesis is the first cyclic process described (1932 Krebs and Henseleit[19]), one in which the idea occurred that synthetic reactions could be achieved through the rapid turnover of carrier compounds in a cyclical manner. Cohen[8] and Ratner[26] have provided the most recent data and interpretations which indicate the nature of these reactions in the ornithine, Krebs-Henseleit or urea cycle.

Ammonia in the liver probably reacts with ketoglutaric acid to form glutamic acid. Glutamic acid by the process of transamination with oxaloacetic acid forms aspartic acid. The last reacts with citrulline to form arginosuccinic acid, which on splitting yields fumaric acid and arginine. The arginine is hydrolyzed to urea and ornithine. The orni-

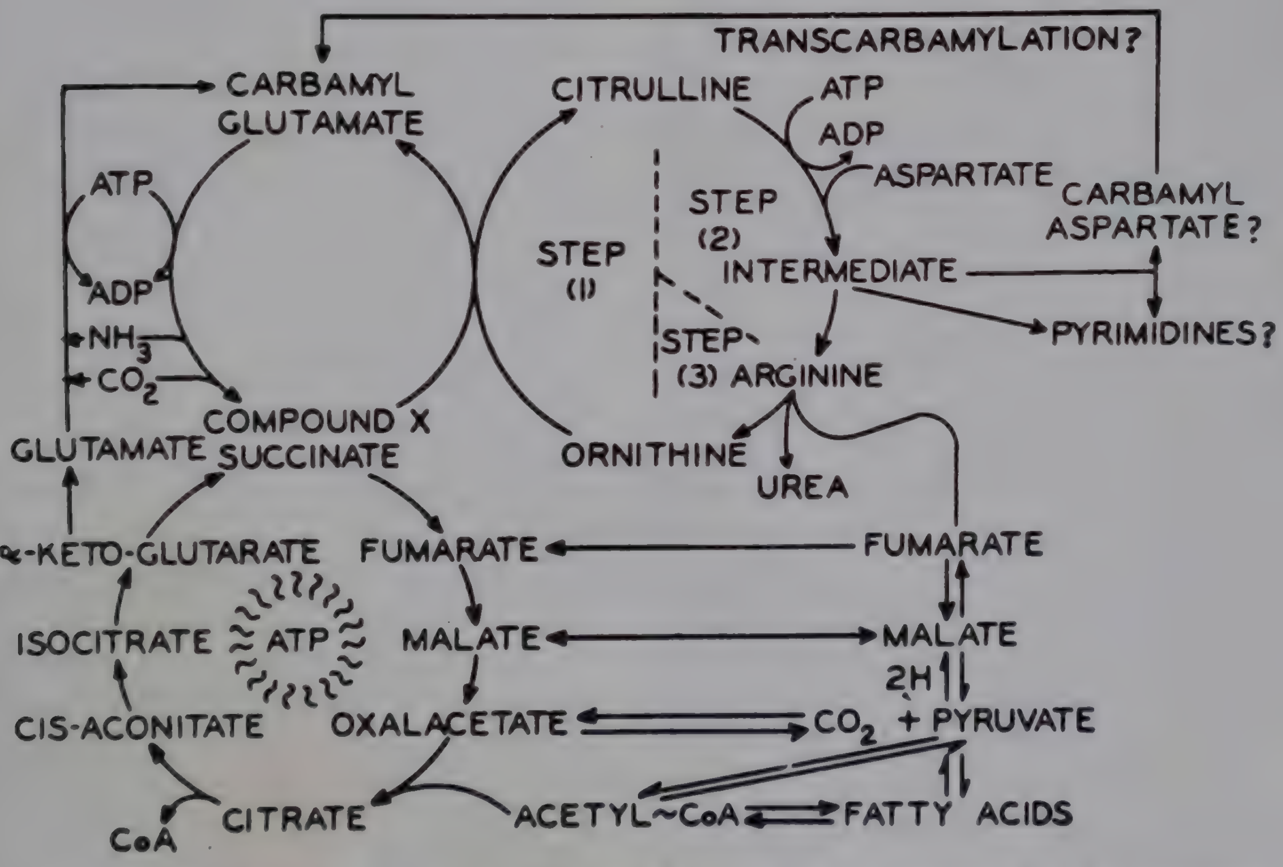

TRANSCARBAMYLATION?
CARBAMYL GLUTAMATE
CITRULLINE
ATP
ADP
ASPARTATE
CARBAMYL ASPARTATE?
ATP
ADP
STEP (2)
STEP (1)
INTERMEDIATE
PYRIMIDINES?
NH3
CO2
STEP (3) ARGININE
COMPOUND X
GLUTAMATE
SUCCINATE
ORNITHINE
UREA
α-KETO-GLUTARATE
FUMARATE
FUMARATE
ISOCITRATE
ATP
MALATE
MALATE
2H
CIS-ACONITATE
OXALACETATE
CO2 + PYRUVATE
CoA
CITRATE
ACETYL~CoA
FATTY ACIDS

Fig. 32. This diagram taken from Cohen[8] shows the mechanism for the synthesis of urea. Ornithine and CO_2 and ammonia which in an active compound, probably carbamyl glutamic acid, react to form citrulline. ATP is required for this synthetic reaction (Step 1). Citrulline reacts with aspartic acid to form arginosuccinic acid (represented above as "intermediate"). This reaction requires ATP (Step 2). Hydrolysis yields arginine and fumaric acid. The arginine is split by arginase to urea and ornithine to complete the cycle while the fumarate enters the citric acid cycle or ultimately the acetyl CoA pool. ATP made in the citric acid cycle is available for the energy requiring reactions in urea synthesis. The other metabolic pathways shown are related intimately to the synthesis of urea and yield or consume intermediates involved in urea synthesis. This is a good example of integrated metabolic pathways.
]

thine is converted to citrulline by a reaction with a glutamic acid derivative, thereby completing the cycle (Fig. 32). The ornithine cycle which consumes ammonia and yields urea is linked as shown above to the citric acid cycle by the process of transamination. In addition the ATP synthesized by the oxidative reactions provides the energy required in these synthetic reactions.

Figure 32 also shows the intimate relationship of the transamination reactions and the citric acid cycle to the ornithine cycle for urea synthesis.

In liver failure ammonia accumulates presumably because of a deficiency of high-energy phosphates which could spark the urea cycle. In liver disease, compounds which provide ammonia and do not provide adequate amounts of ATP simultaneously are likely to lead to an accumulation of ammonia and the resultant toxic state to be mentioned below. In certain liver diseases diets high in protein can produce the meat intoxication syndrome by yielding large amounts of ammonia. Feeding urea or ammonia can lead to similar distress. All these may cause accumulation of ammonia because of inability of the liver to remove the ammonia adequately by the series of reactions described above.

DETOXICATION MECHANISMS IN THE LIVER

As outlined above, the main metabolic functions of the liver are the anabolic and the catabolic intermediary metabolic reactions of proteins, fats, carbohydrates or their derivatives. Other compounds than these enter the body and in the main are metabolized in the liver and excreted via the kidneys. In general, detoxication can be defined as the metabolism of compounds other than carbohydrates, fats and proteins.[43] For example, the metabolism of the aromatic ring of benzene to phenol would be classified as a detoxication reaction, while the metabolism of the aromatic ring of phenylalanine is not detoxication. Most of the end products of detoxication are less noxious than the original ones but not necessarily so. Detoxified substances may have pharmacologic properties.

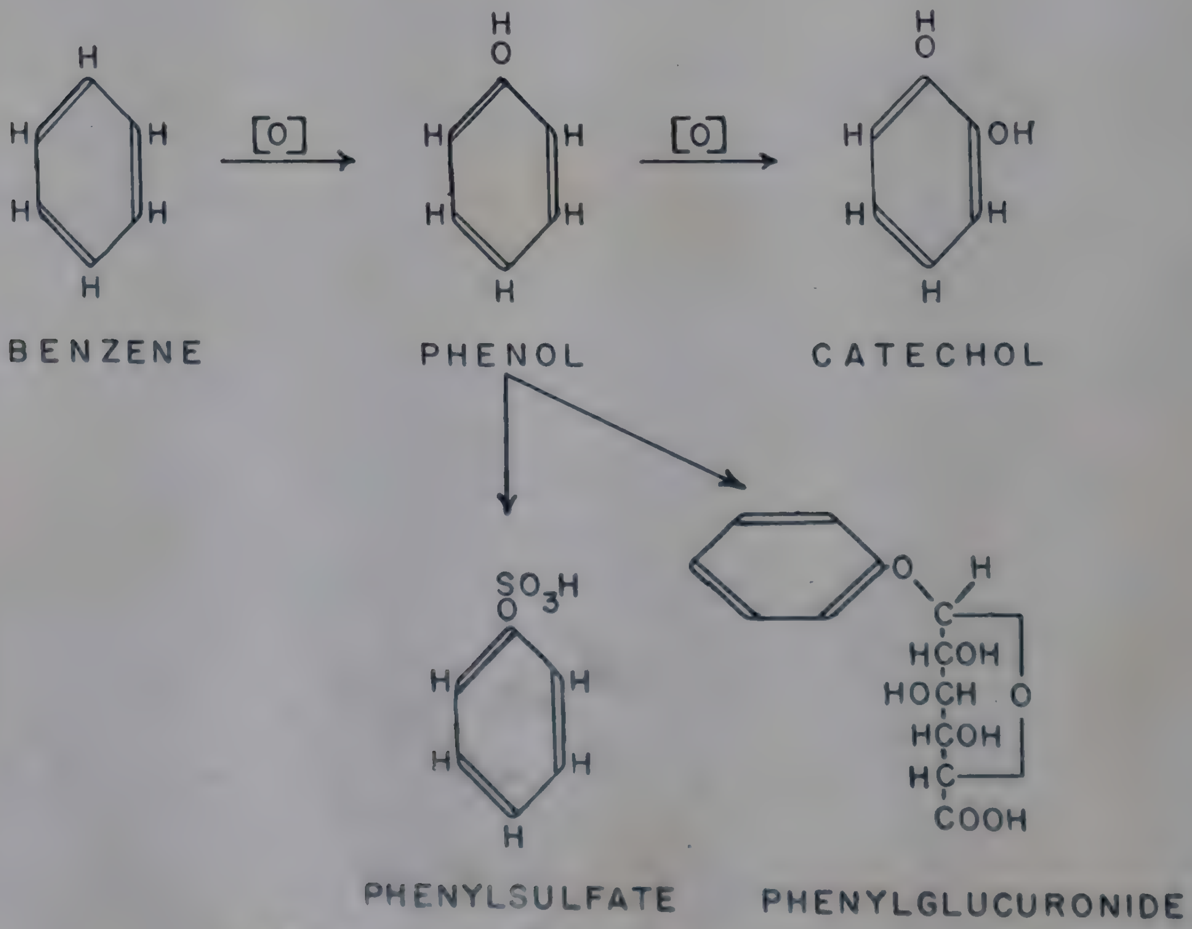


FIG. 33. Detoxication products of benzene.

The detoxication reactions in general are nthetic, examples of which are mentioned low:

- Glucuronic acid conjugation (e.g., benzoic acid or borneol)
- Ethereal sulfate conjugation (e.g., phenols)
- Glycine conjugation (e.g., benzoic acid to form hippuric acid)
- Cysteine conjugation or mercapturic acid synthesis (e.g., bromobenzene)
- Glutamine conjugation (e.g., phenylacetic)
- Acetylation (e.g., *p*-aminobenzenesulfonamide)
- Methylation (e.g., pyridine)

These synthetic reactions by and large are nown to require energy to make them go. or example, hippuric acid synthesis occurs rough the formation of the high-energy enzoyl CoA derivative, while acetylation quires acetyl CoA. Methylations are per- rmed through active methionine. These actions undoubtedly are co-ordinated or oupled with reactions (of the citric acid ycle and so on) which produce high-energy nosphates. A failing liver as in hepatic oma should have a reduced ability to de- xify through the above reactions merely ecause of a deficiency of high-energy com- ounds. An analogous situation is the re- uced capacity of the dog liver to remove nmonia during shock. Here all the enzymes e available, and cellular organization is tact; however, with inadequate oxygena- on of the liver, the oxidative systems can- ot make sufficient high-energy phosphates or ammonia synthesis. The same is probably ue for the synthetic detoxication reactions.

Some oxidative reactions in detoxication e exemplified by the hydroxylation (oxida- on) of benzene to form phenol and cate- ol (Fig. 33). Phenol can be conjugated in e liver and other sites with sulfate to form e sulfate ester. Also, it may be conjugated ith glucuronic acid.

Some compounds are reduced in the proc- s of detoxication. For example, chloral is duced to the corresponding alcohol and is creted as the glucuronide.

Man consumes a number of compounds hich need to be detoxified. In addition, the bacterial flora in his intestinal tract act upon amino acids to produce phenols, indole, skatole, organic acids, histamine, tryptamine, tyramine and other amino acid breakdown products. Man also consumes numerous medications. These compounds pass to the liver via the portal vein where the above reactions occur. In general, the detoxified product is one which is excreted readily by the kidney. In uremia these products of detoxication which are generally anionic accumulate in the blood and contribute to the acidosis. In the main, however, they are not very toxic. In liver failure, particularly if the kidney functions poorly, the undetoxified products accumulate to the point of causing neurologic symptoms. In uremia, ammonia does not accumulate in the blood, whereas in some cases of hepatic coma it does accumulate. The depression of hepatic coma may be deep without marked elevation of ammonia. This suggests that the other products may have a profound effect.

The liver, then, plays a major role in protecting the body from the normal inflow of toxic chemicals.

The excretory function of the liver is poorly understood as compared with that of the kidney. The mechanism by which the dye bromsulfalein is detached from serum albumin and then excreted into the bile is quite obscure. It would seem that cellular work would be necessary to achieve this function. The mechanisms of the excretion of bilirubin, bile acids, cholesterol and other substances remain to be explained. The clinical value of the bromsulfalein test is indeed great, even though the knowledge of its handling by the liver is small.

SOME SPECIAL PROBLEMS OF LIVER METABOLISM

In this chapter biochemical abnormalities which lead to diseases in man have been mentioned. For example, the liver appears to play an important role in the development of atherosclerosis in that it synthesizes more cholesterol from acetate than is needed. It has been suggested that the liver synthesizes more uric acid in gout than the kidney can excrete. Several diseases of metabolism in which the liver is involved have been mentioned. Undoubtedly, in any disease where carbohydrates are used inadequately, or in wasting disease where nitrogen is lost, the liver is affected adversely as suggested above under the carbohydrate and protein discussions.

HEPATIC COMA
(See also Chapter 9)

The syndrome of hepatic coma deserves discussion in terms of the data and postulations presented above. The gastro-intestinal flora produce many toxic chemicals which enter the portal blood and flow to the liver or around it. When the liver fails to detoxify these agents they accumulate in blood and are carried to other tissues. The compounds which the flora metabolize that ultimately may be detrimental are mainly amino acids and urea. The amino acids enter per os or by diffusion across the intestinal wall. Urea is one of the chemicals of the body which diffuses uniformly through the body water and hence into the gastro-intestinal tract where bacterial ureases hydrolyze it to ammonia. The amino acids of the intestines also may be deaminated oxidatively to form ammonia. The ammonia is carried to the liver via the portal blood, where normally it is converted to urea by several energy-requiring reactions. The failing liver is unable to replenish its store of high-energy bonds, hence removal of ammonia by conversion to innocuous urea is incomplete. Ammonia increases in the peripheral blood and is carried to the brain and other tissues. Presumably, in the brain, the ketoglutaric acid of the citric acid cycle is aminated by this ammonia, to form glutamic acid and glutamine. Following hepatectomy in the dog, brain glutamic acid and glutamine double and quadruple respectively.[11] In addition, Bessman et al.[3] have shown the uptake of ammonia by the brain in hepatic coma. If ketoglutarate is being removed from the brain in this manner, it is conceivable that this leads to depletion of the citric acid cycle of the brain and thereby diminishes regeneration of ATP in the brain. Wechsler[41] has found a normal blood flow in hepatic coma but reduced oxygen utilization by the brain, which suggests that this mechanism may be true. Rechnagel and Potter[27] have added ammonia to liver slices and noted the inhibition of the citric acid cycle because of removal of the keto acids by amination. Failure of the liver to detoxify other noxious agents such as phenols, amines, indoles, organic acids and so on could contribute to central nervous system symptoms and abnormal electroencephalograms. In some cases of hepatic coma the blood ammonia is not elevated abnormally. These agents not detoxified by the liver may be contributing to hepatic coma even when ammonia is not elevated.

The failure of the liver to remove ammonia from the blood in hepatic coma in most cases is the result of advanced scarring of the liver with inadequate functioning parenchyma remaining. In the dog in shock where liver cells were intact but hypoxic, it was found that ammonia accumulated in the blood. (This appears to be true in man.[29]) It appeared that the ammonia was coming mostly from the portal vein and to some extent from the kidney but that the liver was not removing it rapidly enough. It was presumed that the hypoxic liver cells could not oxidize substrates to produce ATP which could be used to synthesize urea from the entering ammonia.

McDermott and Adams,[20] and Phillips et al.[24] have shown that feeding sources of ammonia such as high-meat diets, ammonium-containing ion-exchange resins, ammonium chloride and urea could cause selected patients with liver disease to go into coma, during which time the blood ammonia rose. On stopping the ammonia, the coma disappeared. Possibly, the development of coma is explained by the inhibition of brain metabolism as suggested above.

Antibiotics on occasion have a salutary effect on hepatic coma. Aside from the possible effect on an ascending bacterial infection of the liver, they may exert their effect on the urea-splitting and other types of bacteria, by their inhibitory action on these organisms. Aureomycin has the ability to uncouple phosphorylation from oxidation. What this affect might be in coma is obscure.

In dogs put into liver failure with portacaval shunts and arterial ligations by the technic of Rappaport, it was found that blood ketoglutarate rose to abnormal levels in 100 per cent of the animals.[14] This abnormality as found in man in hepatic coma and most equently in liver disease in general.[30] From theterization studies in man it appears that etoglutarate and pyruvate are brought to e liver from peripheral tissues. The liver kes up these keto acids as shown by a positive arteriovenous difference.[31] It seems that liver failure or in liver disease ketoglutaric nd pyruvic acids accumulate because of adequate removal or oxidation by the liver. the author's limited experience ketoglu- ric acid and pyruvic acid were always ab- ormal in hepatic coma, whereas ammonia as less frequently abnormal.

METABOLISM OF ALCOHOL

The metabolism of alcohol by the liver nd its relation to liver disease always has een an intriguing problem. The author and olleagues[32] studied 4 men who had been iven the equivalent of 3 ounces of whiskey travenously. Blood entering and leaving e liver showed an increase in pyruvate and etoglutarate utilization and a drop in citric cid output by the liver while there was a multaneous sharp increase of lactic acid roduction. This was accompanied by a mild cidosis with accumulation of volatile organic cids, presumably acetic acid. These changes ere not observed when equal amounts of lucose (50 Gm.) and amino acids were fused simultaneously. In vitro studies have own that alcohol is oxidized in the liver y 2 dehydrogenation reactions with DPN s the coenzyme. The hydrogen and the elec- ons are transported to pyruvic acid, yield- g lactic acid. A sharp rise of lactic acid nd a fall in pyruvic acid coming from the ver in the human experiments suggest that is mechanism occurs in man. Removal of yruvic acid and presumably the accumulation of reduced DPN could have led in these ases to a reduction in activity of the citric cid cycle and a reduced reservoir of ATP. hat this may be true was suggested by a simultaneous diminution of urea output by the liver. Other data, such as the reduced galactose tolerance during alcohol ingestion, suggest this also. The acidosis also may reflect a reduced ATP pool. In summary, the proposed mechanism of metabolism of alcohol in man is that the oxidation by dehydrogenation proceeds so rapidy that hydrogen and electron acceptors are used so fast that the citric acid cycle in the liver is depleted temporarily, which results in a reduced ATP pool and reduction in the rate of ATP-dependent reactions. If alcohol has an adverse effect on the liver it might be after prolonged use with the resultant prolonged depletion of the citric acid cycle.

SUMMARY

Some of the biochemical reactions occurring in the liver of man and animals have been reviewed. Some defects of metabolism have been mentioned, and possible implications in disease states have been made. The understanding of liver disease and possible therapeutic advances must be made on a rational basis, which means the understanding of the limiting reactions of the liver. While the current liver function tests are valuable clinical guides because of their correlation with liver disease, they are unsatisfactory in defining the primary metabolic defects. New tests are needed to define the various important reactions of the liver, the failure of which may cause disease of the liver or other organs. These will be forthcoming with the understanding of the biochemical functions of the liver. It goes without saying that these advances will lead to therapeutic advances. Since many tissues perform reactions that occur in the liver, the possibility exists that surgical technics such as the portacaval shunt coupled with special dietary therapy may make it possible for peripheral tissues to take over some biochemical duties and thus spare a failing liver.

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Chapter 4

EXPERIMENTAL HEPATIC INJURY

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The liver has been the object of intensive investigations by experimental morphologists, biochemists, physiologists, pathologists and cancerologists. These multidisciplined attacks have produced a volume of knowledge on the subject of hepatic injury that has enabled experimental pathologists to produce in animals close morphologic counterparts of many forms of liver disease encountered in man and to follow their pathogenesis in detail. Advances in the field of experimental hepatic injury have been especially rapid during the past 2 to 3 decades. Many diseases of the liver that commonly had been regarded in the past as either infective or toxic in origin can now be produced in animals by dietary deficiencies. Rapidy accumulating evidence now makes it appear likely that abnormal or insufficient diets may be the commonest cause of liver disease throughout the world. The cause of not only cirrhosis but also primary liver cancer in man may prove to be in most cases a deficiency of one or more essential components in the diet, particularly in the cases of many people in the "protein-poor" parts of the world. Now it has been established beyond any reasonable doubt that cancer of the liver in experimental animals can result from dietary choline deficiency. In a recent review, Tannenbaum and Silverstone[315] suggested that severe dietary deficiencies might be added now to the list of general means of inducing carcinogenesis, the first 3 being physical, chemical or parasitic agents. Neoplasia as the product of a dietary deficiency per se is a relatively new and arresting concept of carcinogenesis.

The history of experimental hepatic injury illustrates particularly the necessity of controlling the dietary background of an animal that is subjected to any experimental procedure. It is quite likely that this principle may hold true for experiments involving other organs, including the kidney and the cardiovascular system. Investigators failed to produce cirrhosis regularly by administration of ethyl alcohol to dogs or rats until the protein background (and thus the lipotropic content) of the diet was controlled. It is now known that the degree of hepatic injury produced by many other agents that are generally regarded as toxic can be altered profoundly by the quantity and the quality of the animal's food intake before, during or after the administration of the toxin. The clinical implications of these discoveries are obvious and far-reaching; they have had an important influence on currently employed therapy of liver disease in man. For this reason, if for no other, the inclusion here of an account of the more important aspects of experimental hepatic injury is justified.

The degree of success with which the experimentalist can reproduce counterparts o disease in man is of immediate interest t the clinician. The present account will dea chiefly with this aspect of experimental hepatology. As dietary investigations have commanded the greatest amount of attention i this field during the past 20 years, they wil be considered first.

EXPERIMENTAL HEPATIC INJURY PRODUCED BY DIETARY DEFICIENCIES

Fatty livers, hepatic fibrosis, cirrhosis, hepatic necrosis and malignant tumors of th liver have all been induced in experiment animals by dietary deficiencies alone. Methods of producing one or more of these lesion "at will" (György) in rats or other anima

ontrolling the composition of the food-
ures they consume have been developed
during the past quarter of a century.
hnics resulting in extensive hepatic dam-
by administration of toxins to a number
species antedated knowledge of dietary
hods by many years. In this chapter die-
hepatic injury will be considered first,
ause information obtained from investiga-
s in this field has altered the interpreta-
s of results of many of the earlier experi-
nts involving toxins. The more recent
rest of the experimental physiologist and
hologist in the effect of diet upon the liver
been reflected by a corresponding in-
ase in clinical emphasis on dietary therapy
hepatic disease in man.

Experiments Concerning the Production and the Prevention of a Fatty Liver

Before 1930 only a few investigators had
ome interested in the apparent protection
rded by some types of diet against de-
opment of liver injury produced by the
ninistration of toxins to experimental ani-
ls.[166, 260, 326] But there had been little evi-
nce to suggest that diet per se could dam-
the liver until the initial observations that
pported this concept were reported in 1930
Hershey[171] in C. H. Best's laboratory at
ronto. Here it was discovered that the
dition of crude lecithin to the diet pre-
nted the accumulation of fat in livers of
pancreatized dogs maintained with insu-
. This report and others that soon followed
naled the dawn of an era in the history of
perimental hepatic injury that eventually
to a number of almost radically new con-
pts regarding several important types of
patic injury commonly encountered in
n. The main events in this sequence of
velopments comprise one of the most in-
esting stories of recent medical research.

In 1889 von Mering and Minkowski[236]
ve the first descriptions of the development
large fatty livers in diabetic depancrea-
ed dogs. Reversal of this type of fatty
er was not accomplished until 33 years
er, when Banting, Best and their associ-
s[15] were able to produce a dramatic mo-
ization of lipid from livers of diabetic dogs
the administration of insulin. Two years
later, however, when more abundant supplies of insulin had become available for use in prolonged studies (7 months) of similar animals, it was found that the hormone had failed to maintain the animals' livers in a state free of abnormal fat.[7, 107] Because the discovery and the production of insulin had made it possible to control the diabetes of completely depancreatized dogs for long periods, the almost equally important discovery was made that lack of *external* secretion of the pancreas was associated with a fatty liver that was unrelated to the lack of endogenous insulin. Raw pancreas fed to the animals prevented the accumulation of fat in their livers. Therefore, it was not unreasonable to assume that this had been accomplished by the presence of digestive ferments in the pancreas that had been added to the diet. But in 1930, Hershey established that crude lecithin incorporated into the food-mixture would accomplish the same protective effect, and it was possible to conclude that under these conditions pancreatic enzymes are not essential to maintain the lives of depancreatized dogs.

Progress in the field was slow at first because many months were necessary for the production of fatty livers in the depancreatized dogs, and not many animals could be studied at one time. These obstacles were largely overcome with the discovery by Best, Hershey and Huntsman in 1932[31] that fatty livers could be produced within a relatively brief period in normal rats fed high-fat, low-protein diets, and could be prevented by feeding lecithin. Advances in the field now became correspondingly more rapid, once it was thus learned that the small, intact rat could supplant the depancreatized dog in further investigations. Best and his co-workers soon identified choline as the active constituent of lecithin[30, 33] because it not only prevented but also cured the fatty livers produced by dietary means in intact rats. Betaine also was found to exert a similar action. Dietary choline proved to be effective in preventing and curing fatty livers of insulin-treated, depancreatized dogs.[26] In 1935 the term *lipotropic* was introduced by Best and Ridout[35, 43] to describe substances in the diet that decrease the rate of deposition and accelerate the rate of removal of liver fat.

In the course of the experiments with rats, it was found that livers of animals consuming a diet of sucrose with 20 per cent added casein did not become as fatty as those of rats transferred to a pure sucrose diet.[21, 34] This finding suggested that casein had prevented a rise in liver fat and in 1935 led Best, Huntsman and Ridout[35] to an understanding of the fact that probably a lipotropic effect was associated with some forms of protein. In the same year Best and Channon[25] published data which established the lipotropic effect of certain proteins. Further evidence of the protective effect afforded by these and other dietary proteins against the accumulation of fat in rats' livers was obtained in 1936 by Best, Grant and Ridout.[27] In the following year, Tucker and Eckstein[317] discovered that the sulfur-containing amino acid, methionine, was responsible for the lipotropic effect of protein, a finding speedily confirmed in a number of other laboratories.[45, 67]

Elucidation of the mechanisms whereby methionine exerts a lipotropic action came from a series of brilliant investigations by Du Vigneaud and his associates. These findings have been summarized by the senior investigator[319] in a paper to which the reader is referred for biochemical and other data. These investigators had reported in 1939[320] that choline plus homocystine, substituted for methionine in synthetic diets fed to rats, enabled the animals to grow. Of other methylated compounds tested, only betaine duplicated this effect of choline. The investigators concluded that choline supplied methyl groups for the in vivo synthesis of methionine from homocystine. As they considered the process reversible, they also concluded that methionine could act as a dietary precursor of choline. By feeding compounds containing labeled methyl groups it was established that metabolism of methionine led to synthesis of choline in vivo by utilization of the labile methyl group from the amino acid. This concept embodies the now well-recognized phenomenon of transmethylation.

Thus by 1930, within little more than a decade and a half following the discovery that the depancreatized dog developed a fatty liver despite insulin therapy, those dietary factors now generally accepted as most important in the prevention of abnormal deposition of liver fat—the lipotropes—had been discovered, and the phenomenon of transmethylation had been established. The stage was set for other important developments in the field, namely, the production of hepatic cirrhosis and malignant neoplasia by dietary deficiency alone. Before considering these lesions, lipotropic factors other than those mentioned above will be discussed briefly.

In 1941 Gavin and McHenry[113] demonstrated that inositol exerted a lipotropic activity in rats consuming a diet containing biotin. During the ensuing decade, a considerable amount of confusion arose concerning the place of inositol as a lipotropic agent in relation to choline and its precursors. Evidence is now available that choline is a more effective lipotropic agent than inositol by itself[32, 38, 48, 214], and that the lipotropic activity of inositol is absent when fat is added to the diet.[48] Inositol and choline together exert a synergistic lipotropic effect[37] but *only* when added to a hypolipotropic diet devoid of fat.[39, 46]

In 1936 Dragstedt and his associates[79] reported that an alcoholic pancreatic extrac which they named *lipocaic* prevented the development of fatty livers in depancreatized insulin-treated dogs. But it now appears tha its lipotropic activity can be entirely accounted for by its total content of cholin and methionine.[44] There is evidence also[2] that the lipotropic activity of another fraction of pancreas described by Entenman an Chaikoff[92] can be explained by the action c its known enzymes whereby lipotropic factors from the various constituents of the die (particularly protein) are made available t the animal. More recently György and his cc workers[144, 277] have described another er zymatic extract of pancreas which exerts lipotropic activity by a similar mechanism.

In 1948 investigations concerning ant anemia factors and other studies resulted i the isolation of the vitamin B_{12}.[279, 305] Tl possibility indicated by earlier investigatio that this vitamin might exert a lipotrop activity under special conditions was co firmed by Schaefer et al.[288, 289] Using rat they found that amounts of choline in tl basal diet too small to prevent complete the accumulation of liver fat were effecti hen vitamin B_{12} was added. Although subequent experiments by Best's group[40] conrmed their observations when all the dieary conditions of the Alabama workers were duplicated carefully, it was demonstrated learly that there were definite limitations to he experimental situations under which the pparent choline-sparing effect of vitamin B_{12} could be observed. A lipotropic effect of B_{12} could not be demonstrated in young, apidly growing rats in the experiments conducted at Toronto.

In both experimental and clinical studies of the effect of dietary deficiencies on the deposition of liver fat and its sequelae (fibrosis, cirrhosis) the importance of total caloric ntake cannot be overemphasized. Early in the Toronto studies[42] it was found that starvation caused a rapid depletion of liver fat n rats maintained on low-choline diets. It has been demonstrated repeatedly that severely hypolipotropic diets will fail to produce appreciable deposits of stainable fat in livers of experimental animals if their caloric intake is very low. Failure to understand the "pseudolipotropic" effect of caloric restriction has led to false interpretations of both experimental and clinical data in which the effect of semistarvation has not been evaluated or understood.[29] The terminal inanition that frequently develops in moribund cirrhotic patients may mobilize almost all abnormal fat from the liver and thus obscure the relation of the fatty and fibrotic lesions. Absence of appreciable amounts of stainable fat in cirrhotic livers obtained at autopsy does not necessarily imply that they represent cases unrelated in their pathogenesis to previous fatty change.

Although it has been demonstrated repeatedly that an abnormally low caloric intake lowers the lipotropic requirement of experimental animals, it has not been demonstrated equally well that caloric intakes above normal will increase the relative demand for choline. Increased caloric intake associated with either high-fat diets[62] or the consumption of alcohol[28, 74] will induce choline deficiency in rats and dogs. Zelman[336] has studied the liver in a series of cases of obese patients and reported that all showed varying degrees of liver injury on needle biopsy, including fatty change and fibrosis in approximately half. These findings are in agreement with those of Sherlock and others.[299] Experimental obesity produced by hypothalamic injury in various species of animals is also associated with fatty liver and cirrhosis.[56] Similarly, fatty livers were found in obesity in inbred mice and in other strains in which the condition was produced by nutritional means.[103, 104] Zelman has concluded on the basis of the observations on experimental obesity in animals and on his own series of obese patients that there may well be an increased requirement of choline and other vitamins imposed by the nature of the obese diet.

A large number of conditions that can affect the lipotropic requirement of experimental animals has now been recognized. Hormones, including cortisone, ACTH, growth hormone, thyroxine, estrogen, are known to influence the animals' demand for lipotropic factor. They will be considered in more detail in a later section. Sellers and You[296] have demonstrated that rats in a cold environment need only a relatively small amount of choline to prevent the accumulation of fat in their livers. This amount of choline was proved to be quite inadequate to prevent fatty livers in comparable animals kept at room temperature. As systematic studies of the effect of an abnormally high environmental temperature have not been reported to date in any publications encountered by the writer, no available data are known that directly support the concept that high temperatures produce high demands for lipotropic factors. But should this prove to be true, it might imply that hyperpyrexia could increase the need for lipotropic factors, a matter of obvious clinical importance.

György[130] has demonstrated that chemotherapeutic agents and antibiotics diminish the animals' needs for lipotropic substances. Popper and his associates in Chicago[184] have found that suppression or alteration of intestinal flora by administration of antibacterial agents to both man and experimental animals results in a decreased conversion of choline in the intestinal tract to the lipotropically inactive compound, trimethylamine. Therefore, increased absorption and utilization of dietary choline would be the expected result of administration of the antibacterial agents, and at first this appeared to explain György's observations. However, it now appears that the excretion of trimethylamine in the animals treated with the drugs returns to normal after a relatively brief period, whereas György's observations indicate that the lipotropic action of antibiotics continues for several months or a year. Nevertheless, the observations of the group at Chicago are of interest in that they have demonstrated that appreciable amounts of dietary choline may be rendered lipotropically inactive in the intestinal tract. Studies of trimethylamine excretion in cases of fatty liver associated with lesions of the intestinal tract in man are indicated by the observations of Popper and his associates.

Clinical evidence that had accumulated over many years has indicated an association between fatty liver (and its sequela of cirrhosis) and the chronic consumption of alcoholic beverages. For a long time it has been debated whether this effect of alcohol is due to a direct hepatotoxic action or to a concomitant induction of a deficiency of essential food factors. Experiments conducted prior to the discovery of the lipotropic factors were inconclusive, probably because inclusion of choline and its precursors in the diets of the animals prevented the development of fatty change and cirrhosis. In 1942, investigators in the U.S. Public Health group[213] found that if the drinking water of rats were replaced with alcohol, the severity of cirrhosis produced in choline-deficient rats was increased. Ashworth[12] later reported an experiment in which it appeared that ethyl alcohol had been directly responsible for producing hepatic lesions, thus supporting the "hepatotoxic school." But his animals were not pair-fed, and their total caloric intakes had not been controlled. Experiments done by the Toronto group in which these factors were controlled[28] indicated that this effect of alcohol is very likely due to the fact that it displaces substances containing lipotropic factors from the addict's diet. Rats given alcohol (15%) in place of drinking water and fed a basal diet containing a known amount of lipotropic factors developed fatty and fibrotic changes in their livers which could be prevented by adequate choline supplements. Similar animals, fed the same basal diet and given sufficient sugar to supply them with the same number of additional calories as were obtained from alcohol by the rats given 15 per cent alcohol in place of drinking water, also developed fatty and fibrotic livers that could be prevented by choline. This experiment indicated that alcohol was no more harmful to the liver than sugar under these conditions, and that in the absence of adequate amounts of dietary choline, sugar could damage the liver as much as alcohol. Although this experiment does not preclude the possibility that commercially available forms of alcoholic beverages may directly damage the liver of man, the evidence strongly suggests that the fatty change and the subsequent fibrosis (cirrhosis) are due at least in part to an induced choline deficiency in alcoholic addicts. For these reasons we have included the effect of alcohol on the liver under the general discussion of fatty liver due to choline deficiency, rather than under the heading of hepatotoxic agents.

Although almost 25 years have elapsed since the publication of the initial investigations that led to the discovery of the lipotropic action of choline, and although more than a century has passed since its first isolation from biologic material by Strecker in 1849, the mode of choline's lipotropic action is as yet unexplained. It appears clear that the liver lipid that accumulates in choline deficiency comes from the diet.[17] Evidence based on the in vivo incorporation of homologues of choline indicates that its lipotropic action depends on the presence of the whole molecule[227, 228] rather than on labile methyl groups.[36] At one time there was much support for the view that choline exerts its lipotropic effect by accelerating turnover of liver phospholipids, but now it has been demonstrated that cystine, cysteine and ethanolamine (none of which are lipotropic) also increase the specific activity and turnover of liver phospholipids.[264] Recently reported observations by Artom[9] indicate that choline may reduce liver lipid by increasing the rate of oxidation of fatty acids. Now he has shown that choline may exert a similar effect on the oxidation of fatty acids in other tissues such as kidney and heart.[10] Recently Gurin[128] has reviewed some of these aspects f fat metabolism and indicated pathways hat may be involved.

There is growing evidence that dietary deiciencies other than choline and its preursors may be associated with the developnent of a fatty liver. But at present none of hese other factors appear to lead to an acumulation of fat as great as that produced y lack of choline. It is even more significant hat none of these other deficiencies have een reported to produce a sufficient or rapid nough accumulation of liver fat to cause tructural changes. To date, only lack of choine has been shown to produce degrees of bnormal fat storage that may be regarded s *harmful* either from a functional or an natomic standpoint. The possibility remains, owever, that in future experiments alteraion of conditions or the employment of some other species may demonstrate that ne or more of the deficiencies mentioned elow may lead to fibrosis or cirrhosis.

In a series of experiments recently reported by investigators at the University of Wisconsin[152, 165] it was found that weanling rats fed diets of 9 per cent casein-sucrose and ll known vitamins, including choline, developed fatty livers that were largely prevented by adding either gelatin or casein. Five per cent casein had the same effect in adult rats.[151] Addition of threonine, glycine, or both these amino acids together, caused a reduction in liver fat. Somewhat similar findings have been reported by Horwitt et al.,[181] using rats and human volunteers. In their experiments accumulation of fat in the livers of rats fed a low protein diet was corrected only by raising the level of dietary protein, supplements of methionine, choline or lysine having little ameliorative effect. Other investigators[310] have shown that forced feeding of an acid hydrolyzed casein diet results in accumulation of liver fat which was prevented by complementing the food-mixture with 0.2 per cent *L*-tryptophane. These and similar investigations indicate that imbalances of amino acids may result in accumulation of small amounts of abnormal liver fat; they suggest that some proteins may exert a greater lipotropic effect than can be accounted for by their methionine-content.[42, 49, 68] Recently, these phenomena have een under study at Toronto,[163] and there is indication that although choline supplements always prevent the accumulation of fat in *centrolobular* regions of the liver, deficient protein or imbalances of some amino acids may result in small amounts of stainable fat appearing in *periportal* areas. It appears that supplements of dietary choline do not influence the fat found in the latter position. Further studies over longer periods of observation and with emphasis on the histologic aspects are under way.

DIETARY PRODUCTION OF CIRRHOSIS

It is not likely that the production and the prevention of fatty livers in animals would have received as much attention as they have from both experimentalists and clinicians if there were not abundant evidence that the fatty liver frequently leads to more serious manifestations of hepatic injury. Clinical observation of the frequent association between excessive deposition of fat in the liver and development of cirrhosis was recorded by Rokitanski several centuries ago.[280] Connor subjected this concept to closer examination by comparing the degree of fat accumulation and the severity of cirrhosis in a large series of cases coming to autopsy. He demonstrated that in the initial stages of the condition abundant amounts of fat were present in the liver, and as the cirrhosis became more advanced the amount of abnormal fat became less.[73] It is now established beyond all question that the fatty liver of choline deficiency may lead to cirrhosis. As cirrhotic lesions become progressively more extensive, the amount of fat in the livers of the experimental animals becomes less, as in Connor's series of human cases. In many other respects, the cirrhosis that develops in fatty livers of choline-deficient animals is the morphologic counterpart of fatty cirrhosis seen in man, particularly that associated with chronic alcoholism.

In some of the earliest studies of the fatty livers of depancreatized, insulin-treated dogs and of livers of choline-deficient rats, MacLean and Best in 1934[217] illustrated and described lesions in which "The number of fibroblasts and leucocytes in these areas was abnormally large," and they also noted that "The liver cords . . . were separated by dilated capillaries and by areas of beginning fibrosis." This description foreshadowed the earliest published report of the development of a definite cirrhosis in depancreatized dogs maintained with insulin, by Chaikoff, Connor and Biskind.[63] Connor and Chaikoff later described the production of cirrhosis in intact dogs in which fatty livers had been produced by feeding high-fat diets and administering alcohol.[74] Soon after the initial report of Chaikoff et al.[63] György and Goldblatt[131] observed the development of cirrhosis in intact rats fed diets deficient in the B vitamins, including choline. In 1940, Chaikoff and Connor were successful in producing fatty livers and cirrhosis in normal dogs fed high-fat diets without alcohol. Other reports confirming the essential nature of the foregoing observations rapidly appeared,[50, 52, 132, 322, 323] and by 1943 it was generally accepted that the fatty liver of choline deficiency in both intact rats and dogs was followed by a grossly nodular cirrhosis which could be prevented by the administration of lipotropic agents in the diet.[52, 211]

By employing choline-deficient rats sacrificed at intervals during the experimental period, it has been possible to follow the pathogenesis of grossly nodular cirrhosis from its very beginning to its final stage. These studies have thrown considerable light on the relation between the fatty liver and the fibrotic liver, and some aspects have had application in the field of clinical pathology. Therefore, the salient features will be summarized here.

The initial pathologic descriptions of dietary cirrhosis in both dogs and rats frequently stated or implied that the distribution of the fibrous tissue was primarily periportal.[51, 131, 278, 322, 323] However, when earlier stages of the lesions were studied, it became apparent that the fibrosis was *initially* nonportal.[11, 117, 134] Recently, we have shown[157] that the smallest terminal units of the portal vein and the hepatic artery never become surrounded by fibrous tissue, and that even in the late stages of the disease fibrosis can be demonstrated only around the large conducting branches of these vessels. Regions around the latter are periportal only in an anatomic sense, because functionally they bear no relation to the entry of fresh blood into the hepatic parenchymal unit. Subsequent studies of livers in alcoholic cirrhosis in man have indicated that the same distribution of fibrous tissue (geographically periportal but *functionally* nonportal) is frequently the rule.

In choline-deficient rats, the accumulation of abnormal amounts of centrolobular fat per se does not lead to fibrosis.[148] Studies of the pathogenesis of the early lesions have shown that the accumulation of fat must be rapid and so excessive that individual parenchymal cells become distended, literally to the bursting point by their contained fat.[155] This type of rupture does not result in immediate death or necrosis of the cells, for they become joined together to form the walls of cysts that for a time at least contain the escaped fat. Further accumulation of lipid within these *fatty cysts* (originally termed "lipodiastaemata") leads in turn to their eventual rupture. When these relatively large structures are torn, the fat frequently escapes from the cysts and from the liver via either biliary canaliculi or blood sinusoids, because often these channels are disrupted by distention of adjacent cysts.[162] Ruptured cysts then collapse and in the process become surrounded by a mass of reticulin which previously supported the cells that comprised the cyst wall. Since up to 60 or more cells may form the walls of large cysts, appreciable amounts of reticulum may become condensed around these structures when they collapse after losing their fat. Repetition o these events—cyst-formation, cyst-rupture and cyst-atrophy—over appreciable period of time in the nonportal regions of the live eventually leads to the formation of island and bands composed of condensed reticulin and remnants of atrophic parenchymal cell that once formed cyst walls. Careful studie of all stages in the formation of the fibrou trabeculae indicate that this sequence events can wholly account for all the fibros that develops in the trabeculae without invoking any actual proliferation of fibrou tissue. There is an increase in the tota stromal content of these livers as shown b biochemical estimations of collagen,[250] bu this increase can be accounted for by th appearance of reticulin fibers around new formed parenchymal cells in the areas mpensatory hyperplasia in the nonscarred gions.

Studies of livers in choline-deficient rats d mice, as well as of alcoholic cirrhosis in an, show that in any section of liver the evelopment of this type of condensation rosis or "reticulinosis" (Sellers) is related nstantly to the regions in which shrunken tty cysts are present. However, the mere rmation of cysts per se is not sufficient r the production of the condensation reticu- nosis; they must first rupture and collapse. ecently concluded experiments at Toronto ave shown that for some as yet unspecified ason cysts in livers of choline-deficient ice do not rupture readily.[160] Instead, they ach relatively enormous proportions, and these livers condensation reticulinosis or brosis does not become as conspicuous a ature as in the choline-deficient rat or alco- olic man. In the choline-deficient mouse, epatomata have been observed to develop eadily (within 5 months) with metastases the lung.[160, 332]

In the past many authors of textbooks ave emphasized that the size of nodules in cirrhotic liver may offer a clue to the eti- logy of the lesion. In so-called "toxic cirrho- is" or "postnecrotic scarring" the nodules re described as large (over 2 cm. in size)— he multiple nodular hyperplasia originally escribed by Marchand (1895). On the ther hand, the liver in alcoholic cirrhosis is aid to exhibit frequently a finer, more even odularity or only a granularity. Observation f the gross appearance of livers of choline- eficient rats in various stages in the development of this type of dietary cirrhosis (with r without alcohol) has demonstrated, how- ver, that the size and the irregularity of the odules become greater as the condition rogresses, so that the two types of livers requently described in textbooks may repre- ent only the appearance in various phases n the development of the same condition.

Restoration of lipotropic factors to cho- ine-deficient rats rapidly mobilizes all ab- ormal intracellular fat—within a matter of ours.[191] Fat contained within cysts, and herefore ipso facto in an extracellular posi- ion is also mobilized eventually by treatment with choline,[164] but this may take weeks or months. Cysts within trabeculae which have not atrophied completely may persist for particularly prolonged periods after treatment has been instituted and long after all other evidences of fatty change have disappeared. The finding of persistent *intratrabecular cysts* thereby offers a possible diagnostic clue at autopsy as to the nature of an arrested cirrhosis in cases where otherwise it might be in doubt as to whether or not originally the lesion was associated with excess fat storage. A survey of the presence of intratrabecular cysts in a series of 95 cases of cirrhosis in man encountered at autopsy has supported this thesis.[156]

Fatty cysts have now been described by a number of observers in various types of cirrhosis in man, including cases of gross dietary deficiencies, obesity and alcoholism[204, 84] and in livers of children with kwashiorkor.[311] The sequence of events related to cyst formation described in the choline-deficient rat has also been followed in the kwashiorkor liver. Elias and Popper[87a] have described fatty cysts in Laennec cirrhosis but emphasize that the liver of man differs from that of the rat in that it responds diversely to excessive accumulation of fat, so that stress fissures and membrane formation after inflammation may also play an important role in explaining the final form of the lesion.

DIETARY PRODUCTION OF HEPATIC NECROSIS

Hepatic injury associated with a simultaneous deficiency of the sulfur-containing amino acids, methionine and cystine, of alpha tocopherol and of a factor in certain yeasts and casein, is dramatic, fulminating and rapidly fatal. Both the clinical picture and the pathology of dietary necrosis are in sharp contrast with the distinctly slower and more insidious onset of the fatty liver and cirrhosis associated with a lipotropic deficiency. Rather suprisingly, distinction between these two types of dietary hepatic injury was not clearly recognized in the early stages of their investigation, and for a time they were confused. The reason for the confusion was due largely to the necessity of employing diets low in methionine (and thus in protein) to produce both conditions. Methionine deficiency is necessary for the production of necrosis in order to keep the level of amino acid and sulfur low in the diet. Methionine must also be restricted in hypolipotropic diets, as it is a precursor for the formation of choline in vivo by transmethylation. However, methionine deficiency is the only factor of any importance that is common to the two types of dietary hepatic injury—necrosis and cirrhosis.

Almost all investigators in this field now generally agree that the first production of acute massive hepatic necrosis in rats by dietary means should be credited to Weichselbaum.[324] In 1935 he described ". . . hemorrhages throughout the liver" in rats that died after being fed a low-protein diet. He reported that 0.2 per cent cystine or a comparable amount of methionine added to the basal diet prevented the animals from dying. The significance of this finding was not fully understood until some years later when György and Goldblatt[131] described acute liver damage (necrosis) in rats fed a diet deficient in the vitamin B complex (but supplemented with thiamine, riboflavin and pyridoxine). The diet employed was low in lipotropic factors so that fatty change and cirrhosis were also present in many of the livers. The authors extended these findings in subsequent publications.[132, 133]

In 1942 investigators in the U.S. Public Health group[76] reported experiments that clarified the distinction between experimental hepatic necrosis and cirrhosis. They found that whereas the lipotropic factors prevented fatty livers and cirrhosis, methionine or cystine prevented necrosis, and choline had no influence on the latter type of lesion. Therefore, they postulated that necrosis and cirrhosis were separate and distinct lesions, each produced by specific dietary deficiencies. Soon this concept was supported by results of other investigators[118, 176, 177] and was in accordance with findings that had been made in Germany a year earlier.[179] In all these diets, yeast was used as a source of protein, and it soon became apparent that the incidence and the severity of the necrosis varied with the source of the yeast.[179, 139, 212] It was concluded either that yeast may contain a substance that protects the animal from hepatic necrosis or that on the other hand some forms of yeast contain a hepatotoxic factor. As pointed out by Beveridge in a recent excellent review on the subject,[47] there must be present a protective factor in yeast, otherwise increasing the level of yeast in experimental diets would not prevent the appearance of acute liver damage as found by a number of investigators.[131, 176, 232] However, Beveridge reports[47] that in one experiment he obtained a much lower incidence of necrosis in rats fed a diet containing alcohol-extracted yeast than in rats fed a diet containing the nonextracted yeast. The author feels that this would indicate ". . . beyond question that some toxic factor had been extracted from the yeast" by the alcohol.

As diets containing yeast generally result in a higher incidence of necrosis than do diets containing comparable amounts of amino-acid sulfur supplied by casein, it has been suggested that casein may contain some protective factor. Schwarz[290, 291] has found that such a protective factor in casein can be demonstrated, and that it can be extracted with alkali. He has termed this casein-factor "Factor 3."[292, 294]

During the next several years, investigators at a number of centers experienced difficulties in producing hepatic necrosis in rats fed diets deficient in sulfur-containing amino acids, and it became apparent that some factor or factors yet unidentified must be playing a role in the production of the lesion. György reported in 1947[129] that the incidence of hepatic necrosis was less when fats containing vitamin E were used in place of lard, and soon it was established by a number of investigators that alpha-tocopherol was effective in preventing the lesion.[1, 2, 134, 178] However, the discovery of the role of alpha-tocopherol in preventing this type of hepatic necrosis in rats should be attributed to Schwarz[290, 291] who reported this fact in 1944 in publications not then available outside Europe. It is apparent then that at least three sets of conditions must apply for the production of hepatic necrosis in rats: the diets must be low in sulfur-containing amino acids, little available alpha-tocopherol can be present, and a protective factor in casein (Schwarz's Factor 3) must be low or absent.

Other factors have been studied to determine their effects on the production of die

ry necrosis of livers of rats. The younger
e rats the more susceptible they are to this
pe of hepatic damage,[5] and males are less
sistant than females.[5, 293] Cortisone injec-
ons afford partial protection;[293] desiccated
yroid accelerates its production.[5, 149, 231]
he level of fat (apart from its tocopherol
ontent) in the diet may exert a profound
fect on the incidence of dietary necrosis.[234]
everidge et al.[47, 234] found that over a
eriod of 15 months when successive groups
rats were fed a fat-free necrogenic diet, all
imals in the first group survived the experi-
ent; but in subsequent experiments there
as a general trend toward an increasing
cidence of the lesions in animals on the
t-free food mixture. He suggests that intes-
nal organisms having an effect on the
roduction of the acute lesion were initially
hibited, due to the altered dietary regimen
fat-free), but subsequently became adapted
that their ability to exert a predisposing
fluence on development of hepatic necrosis
as restored. This concept is supported by a
milar series of findings by György et
l.[141, 142, 143] who found that when Aureomy-
in was used in successive experiments, it
radually lost its antinecrogenic property.
his observation is supported by results ob-
ained with feeding necrogenic diets to
erm-free rats, for the latter lived twice as
ong as control rats (not germ-free) fed the
ame diet.[142]

Exhaustive studies of animals killed at
ntervals after they have been fed the necro-
enic diets have failed to elucidate the
athogenesis of the hepatic lesions which
ppear, after a variable and sometimes
engthy latent period, with dramatic swift-
ess. Although these investigations have in-
luded histologic,[3, 6] biochemical,[4, 202] enzy-
atic[124, 253, 257, 258] and hematologic[281] stud-
s, none have uncovered the factors that
xplain *why* this certain combination of
ietary deficiencies produces sudden death
rom hepatic necrosis in rats. Hove, Cope-
and and Salmon[183] reported that the hepatic
ecrosis was associated constantly with pul-
onic congestion and hemorrhage. The fact
hat in these animals there is evidence of
irculatory disturbances—congestion and
emorrhage—in the two large organs on
ither side of the heart in terms of blood flow would suggest to this reviewer that closer examination might be made of the hearts of rats in which hepatic and pulmonic lesions have developed. This certainly would be the usual reaction of the clinical pathologist who discovered a similar combination of lesions at routine autopsy. Cardiac involvement might well explain some aspects of the little understood protective action of tocopherol in the experiments with rats.*

An investigation of particular interest to clinicians is that conducted by Hoffbauer and Wittenburg.[180] They produced repeated sublethal episodes of dietary hepatic necrosis in rats by giving the animals short courses of protective substances whenever bilirubinuria indicated that they had developed an attack of necrosis. At autopsy the animals exhibited only postnecrotic scarring or massive necrosis or both, but cirrhosis was never present. The authors conclude that repeated attacks of necrosis of the liver are unlikely to be a cause of cirrhosis in man.

In his recent review of acute liver damage and diet, Beveridge concluded that it is impossible to say at present that there is any connection between the lesions seen in rats and hepatic necrosis (acute yellow atrophy) in man. We concur entirely with the caution expressed in this view and agree that application to the field of human liver disease must await further investigation.

DIETARY INDUCTION OF MALIGNANT TUMORS OF THE LIVER

In recent reviews Tannenbaum[314, 316] has emphasized that until 1946 experiments on diet and the nutritional state of the host were studied only as *modifiers* of carcinogenesis initiated by other means (physical, chemical or parasitic). Only recently have dietary deficiencies been regarded as possible *initiators* of neoplasia. One example of the latter circumstance is afforded by the development of papillomatosis of the fore-stomach of rats deficient in vitamin A, although this may not represent true neoplasia,[illegible] and the growths almost certainly are not malignant. The second example concerns the occurrence of malignant hepatic tumors in choline-deficient rats, chickens and mice. There appears to be little doubt at the present time that the growths induced by choline deficiency in livers of at least these 3 species represent true neoplasia.

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* Prof. J. M. R. Beveridge of Queen's University, Kingston, demonstrated to the writer some years ago the presence of cardiac necrosis in sections of hearts of young rats that had been fed a "necrogenic" diet. Very recently, Williams and Aronsohn at Minnesota[331] have reported extensive myocardial lesions in over 70 per cent of 99 mice fed a British yeast diet of the type first employed by Himsworth and Glynn.[176] Dr. M. R. Abell, then of the University of Western Ontario, London, collaborated with Dr. Beveridge in the experiments cited here.

For a long time authors of textbooks have recognized that an association exists between hepatomata and cirrhosis in man. With the production of cirrhosis in a variety of species by choline-deficient diets, therefore, it was perhaps not altogether unexpected to discover tumors in cirrhotic livers in susceptible strains of animals subjected to a deficiency of lipotropic factors. The first reported occurrence of tumors in choline-deficient rats came from the laboratories of W. D. Salmon at Alabama in 1946.[78, 92] These investigators discovered hepatomata in 10 per cent of rats fed a low-choline diet for periods of 8 to 16 months and neoplasms resembling adenocarcinomata in livers of 30 per cent. Some doubt was expressed at first by other investigators as to whether or not the nodules represented true neoplasia or merely very active foci of compensatory hyperplasia in the cirrhotic livers. Although at least one report appeared[illegible] in which other investigators had failed to observe tumors in rats fed low-choline diets for prolonged periods, it soon became apparent that the species of rat employed was responsible for the apparent lack of agreement, some species being much more susceptible than others.[illegible] Investigators in Europe soon confirmed the findings of the Alabama group, for they reported the development of multiple adenomata in livers of choline-deficient rats within relatively short periods.[illegible] Subsequently, Salmon's group repeated their observations in larger groups of rats[illegible] and investigated the possible secondary effects of other essential food factors. They found that riboflavin would prevent the induction of hepatic tumors associated with feeding low-choline diets and they compared this anticarcinogenic property of riboflavin with its action in p
ing liver tumors induced by aze
Schaefer, Copeland and Salmon
ported the production of neoplasms in
ens following prolonged dietary
deficiency.[illegible] Any remaining doubt
ing the malignancy of the liver les
now been dispelled by the demonstra
metastases of the hepatic tumors
lungs.[illegible] Only recently in Toronto w
observed the development of hepatic
in choline-deficient mice with p
metastases in at least one instance w
period of less than 5 months.[illegible] The
now feels that there is no doubt that
deficiency may induce malignancy in
of susceptible animals. These finding
support the view that tumors arise,
stimulation of normal cells, but as an
tation to conditions that injure and
the growth of normal cells, a view
outlined by Tannenbaum.[illegible] It wo
pear that severe dietary deficiencies
be added to the list of conditions kn
produce cancer in experimental an
might not be too rash to link this
with the high incidence of primary liv
cer in populations of the "prote
parts of the world.

EXPERIMENTAL HEPATIC IN INDUCED BY TOXIC AGEN

Apart from surgical interference,
production of experimental hepatic
was accomplished by the administ
substances which proved to be direct
to liver cells. In a recent excellent re
the subject, Drill[illegible] cites work by
baum[illegible] as early as 1882 in wh
injury was produced by administra
arsenic or phosphorus. The hepato
tion of chloroform in man had bee
nized even before this in 1850,[illegible]
ready mentioned, the advent of kn
during the last 2 decades concer
production of hepatic injury by
means has necessitated considerable
of the views of experimentalists an
cians alike on the mechanism of a
hepatotoxic agents. In his review,
considered these aspects of liver
relation to toxins,[illegible] and the read

TABLE 3. COMMON HEPATOTOXIC AGENTS USED IN EXPERIMENTAL PATHOLOGY

NAME	LESIONS THAT HAVE BEEN PRODUCED	REFERENCES
Amanita phalloides toxin	Fatty degeneration	57
	Necrosis	
Arsenic	Centrolobular necrosis	110, 115, 116, 194
	Fibrosis Cirrhosis	197
Azo compounds	Cirrhosis and cancer	241 (rev.)*
BAL (2-3-dithio-propinol)	Necrosis	219
Benzene	Fatty change	208, 209, 210
Bromobenzene	Fatty change	190, 192, 329
	Periportal fibrosis	
Carbon tetrachloride	Fatty change	54, 59, 97, 105
	Centrolobular necrosis	146, 174, 197
	Cirrhosis (nonportal)	223, 238, 248
	Cancer	
Chloroform	Fatty degeneration	96, 223, 248, 256
	Centrolobular necrosis	259, 325, 327
DDT (dichlorodiphenyltri-chlorethane)	Fatty change	199
	Necrosis	
Ethionine	Fatty change	83 (rev.)*
	Hyperplasia and tumor	
	(Pancreatic degeneration)	
Ethylene dichloride	Fatty degeneration	168, 169, 200, 254
Ethyl urethane	Cirrhosis; cancer	186
Lead	Necrosis; cirrhosis	70, 115
Phosphorus	Fatty change	41, 220, 261
	Periportal necrosis	
	Fibrosis; cirrhosis	
Propylene dichloride	Centrolobular necrosis	167, 173, 331
Pyridine	Fatty change	18, 19, 20
	Cirrhosis	
Selenium	Fatty change	252 (rev.)*
	Necrosis	255, 297
	Cirrhosis; cancer	
Sodium tannate	Necrosis; cancer	154, 195, 196
Trinitrotoluene	Fatty degeneration	175, 249, 308
	Centrolobular necrosis	

hese references review the literature on the subject.

d to his comprehensive monograph for
ore detailed discussion of the subject
can be given here.
e list of hepatotoxins is now long, and
xperimentalist who wishes to produce
injury in an animal has a wide choice
ents. The type and the extent of the
ing injury will vary with the dose and
nanner in which the agent is introduced
the animal. Lesions that can be pro-
d include minimal fatty change, zonal
assive necrosis, diffuse fibrosis, cirrho-
nd frank neoplasia. No attempt will be
in this chapter to discuss each of these

many hepatotoxic agents in detail. The more important ones are listed in Table 3 with key references that may be consulted for experimental data. The references cited have been chosen on the ground of either priority or comprehensiveness and include only a few of the many available on each agent.

The dietary background of the animal will modify the response of its liver to most hepatotoxic agents, particularly those given by mouth. Especially during the past 10 to 20 years, the effects of variations in the composition and the quantity of the diet fed to animals treated with hepatotoxins have been tested in a large number of reported experiments. It would be out of place here to attempt to review all these investigations in detail, as Drill has considered them recently *in extenso*.[80] However, from the wealth of information available, a pattern appears to be emerging concerning the relation of diet to hepatotoxic injury.

In the earlier sections of this chapter, hepatic injury produced by dietary means alone (cirrhosis, necrosis) has been discussed. It now appears that most dietary conditions that per se tend to produce injury of the liver often will increase the animal's susceptibility to hepatotoxins, although there are, of course, exceptions. Thus, a high-fat diet will increase the susceptibility of animals to chloroform,[260, 261, 262] to carbon tetrachloride,[70, 109, 140] to organic arsenicals,[237] to propylene dichloride[167] and to trinitrotoluene.[175] A high-protein diet will afford protection against chloroform,[78, 247] against benzene[209] and against selenium in the diet.[207, 251, 306, 317] Protein depletion, on the other hand, increases the susceptibility of animals to chloroform,[244] pyridine[18] and benzene.[208, 210] Methionine supplements in diets fed experimental animals afford measures of protection against liver damage produced by administration of a number of agents, including chloroform,[243, 245] propylene dichloride,[167] benzene,[209] bromobenzene,[190, 192, 329] trinitrotoluene,[308] pyridine[20] and oxophenarsine.[121] Dietary methionine supplements also afford protection for rats fed a low-protein diet containing selenium, provided that adequate amounts of alpha-tocopherol are available in the diet.[297] Vitamin E or methionine added to a low-casein diet (10%) decreases the mortality of rats exposed to carbon tetrachloride.[182]

Diets containing high levels of carbohydrate have been found to afford protection to animals against chloroform,[78, 123] carbon tetrachloride[77, 53] phosphorus[261, 276] and certain arsenates.[116] However, Drill points out that many of these results may be regarded as due more likely to an associated decrease in hepatic lipid,[80] because Goldschmidt, Vars and Ravdin[120] found no difference in the degree of liver damage in rats with high and low liver glycogen, respectively, when equal concentrations of hepatic lipids were present in both groups. As the toxic action of many agents is enhanced in animals fed high-fat diets, it might be expected that choline would afford increased protection against hepatotoxins. Although this appears to be true in the case of ethylene dichloride,[168] if choline plus cystine are added to a low-protein diet, choline alone is without effect.[276] Furthermore, choline alone fails to provide protection against the administration of chloroform,[120] carbon tetrachloride[170, 276, 295] and phosphorus.[41] Nevertheless, it has been shown that adequate supplies of lipotropic factors must be present in the animals' diets for recovery from carbon tetrachloride and phosphorus to take place after exposure to the toxins has been completed.[16, 41, 295] Fasting renders animals more susceptible to the liver damage induced by chloroform[78, 120, 247] and decreases the rate of regeneration of liver following injury.[304] The influence of antibiotics and chemotherapeutic agents in increasing the resistance of rats to chloroform,[108] carbon tetrachloride[201] and other toxins may act through altering the intestinal flora and thus the intestinal absorptio of amounts of protective substances presen in the ingested food.

Investigations employing radioactive carbon tetrachloride[229] administered to monkeys have indicated an affinity of the chemical for fat, although information is no available concerning the concentration o similar materials in the liver at different levels of fat storage. This may suppor the explanation, originally suggested b Wells,[325] that the increased susceptibility t chloroform associated with a fatty liver ma be due to a greater hepatic concentration c the toxin than would be found in the norma liver. The fat within liver cells may dissolv and store fat-soluble materials and maintai a harmful level within the organ for a longe period of time. MacNider[218] was impresse with the increased resistance that liver cel appear to acquire in animals that had bee exposed repeatedly to a variety of toxins. W have found in studies of regeneration noc ules in cirrhotic livers of choline-deficier rats that the amount of fat present in th newly formed tissue is invariably small, eve though animals remain on the hypolip tropic regimen. It is possible that a simil resistance to fatty change in cells of live in animals studied by MacNider might a count for their comparatively greater immunity to hepatotoxins, since the concentration of the latter within regenerated livers may not attain as high levels as when animals are exposed initially to these agents, owing to differences in liver fat under the two conditions.*

There is probably little doubt that, under some circumstances at least, the protective action of high-protein diets, or diets supplemented with methionine, may be attributed to their ability to supply sulfhydryl (SH) groups. It is possible that some toxins may produce hepatic injury by inactivation of sulfhydryl groups. As dietary hepatic necrosis is associated with a deficiency of cystine and methionine, Drill[80] has suggested that hepatic necrosis of dietary origin may have a common basis related to a reduction of sulfhydryl groups caused by various hepatotoxic agents, vitamin E deficiency or cystine deficiency.

Various theories and hypotheses have been suggested in the foregoing paragraphs to explain the protective action of certain types of diets against damage to the livers of animals that have been given hepatotoxins. There is probably no single explanation at hand that will account satisfactorily for all the known facts. However, the available data serve more than adequately to emphasize again the need for the clinician to pay careful attention to the composition of the diet and the caloric intake of patients who are suffering from almost any form of hepatic disease.

In Table 3 bromobenzene and ethionine have been listed as hepatotoxic agents, although probably it is more nearly correct to call them antagonists of the amino acids, cystine and methionine. Ethionine has been shown to inhibit the conversion of radioactive methionine to glycine[101, 302] and to become incorporated into proteins of an abnormal type.[235] Rats treated with ethionine develop a fatty liver within 24 to 48 hours in adult females[302] but not in adult males.[98, 99] Almost simultaneously, Farber and Popper,[100] in Chicago, and Goldberg, Chaikoff and Dodge, in California,[119] reported the destruction of acinar tissue in the pancreas as early as 12 hours following a single injection of ethionine. The lesions were initiated by loss of cytoplasmic basophilia of the pancreatic acinar cells followed by diffuse pancreatitis. Subsequently, the investigators at Chicago studied the changes in livers of rats subjected to chronic ethionine feeding for a period of 28 days.[193] Fibrosis and cellular damage of the liver (as well as pancreatic acinar atrophy and fibrosis) were present in rats of both sexes. Parenchymal liver cells were enormous with multiple nuclei and large, eosinophilic nucleoli.[266] In 1953 Popper et al. were able to report the development of hepatic tumors due to prolonged ethionine feeding,[265] although the authors felt that the malignant nature of these growths was debatable. Other investigators have studied the effects of ethionine in dogs, cats and monkeys,[8] and although interesting changes were described in other organs, including the pancreas and the gastro-intestinal tract, lesions other than fat accumulation were not encountered in livers of animals in these experiments. Ethionine administration has also been found to retard the growth of transplanted fibrosarcomata in both male and female rats.[206]

HEPATOTOXIC AGENTS AND THE PRODUCTION OF EXPERIMENTAL CANCER OF THE LIVER

The importance of the role of the animal's diet as a factor influencing the production of liver tumors by feeding carcinogenic amino-azo dyes became apparent shortly after the demonstration by Yoshida in 1933[285, 335] of the hepatocarcinogenic activity of *o*-amino-azotoluene. Attempts by investigators in Germany[166] to confirm this observation failed largely because of the nature of the diet used, which since then has been shown to be partly protective. Then related compounds were tested for carcinogenic activity, and in 1937 Kinosita[189] produced liver cancer in 150 days using *p*-dimethylamino-azobenzene (Butter Yellow). Since that time derivatives of this dye have been found to exert a similar carcinogenic activity and have been used in recent studies.

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* Only very recently, Wilson, of Providence, has demonstrated[332] that the apparent resistance of liver cells in hyperplastic nodules and tumors induced in livers of mice by repeated carbon tetrachloride administration may be explained by their blood supply. Necrotizing doses of carbon tetrachloride failed to affect these nodules and tumors, although the rest of the liver responded typically. But transplants of these tumors (which were well vascularized) exhibited no more resistance to the hepatotoxin than did normal liver tissue. Wilson relates these findings to those of Breedis and Young[55] and others who have shown that liver nodules and tumors are supplied by branches of the hepatic artery only.

The histologic changes in livers of rats fed azo dyes have been reviewed recently by Miller and Miller.[241] The appearance of tumors is preceded by the development of a grossly nodular cirrhosis (Laennec type) after the animals have been fed the dye for 4 to 4½ months.[313] The earliest histologic changes detected have been regarded as the first stage in carcinogenesis, but obviously these changes could be related instead to the liver cell damage that subsequently becomes manifest as cirrhosis. If feeding of the dye is discontinued after the appearance of grossly nodular cirrhosis (determined at laparotomy) the cirrhosis then regresses, and the tumors grow to an easily recognizable size. Both the origin and the histologic classification of the tumors have been the source of considerable debate, some investigators regarding them as hepatomata and adenocarcinomata, while others have classified them as cholangiomata or mixed types. Metastases, particularly to the lung via the blood stream or to the mesentery by direct extension, are observed relatively commonly. A number of investigators have confirmed the demonstration by Breedis and Young[55] that the tumor nodules (as is the case for nodules of hyperplastic parenchyma in cirrhosis) receive their blood supply entirely from branches of the hepatic artery.

Because of the recognition in 1935 of the importance of the dietary background in the production of liver tumors by feeding azo dyes, the ensuing 2 decades have witnessed a host of investigations into this relationship. The voluminous literature on this subject has been reviewed recently in several places.[80, 241, 314] Caloric restriction per se has been shown by Tannenbaum and Silverstone to inhibit the formation of benign hepatomata in mice.[315] Riboflavin (approx. 100 μg. per rat per day) has been found by a number of investigators to inhibit the speed with which the azo dye tumors appear, confirming the initial report of Kensler et al. in 1941.[188] Cystine supplements to diets containing the dye under the conditions generally studied have resulted in a decreased tumor incidence,[135, 153, 242] although the effect has not been demonstrated on very low-protein diets. Methionine supplements[242] exerted a similar influence, but, although choline added to the experimental diets reduced the degree of cirrhosis, it had little or no effect on the tumor incidence.[58, 82, 85, 240, 246, 328] The converse effect was obtained by feeding nicotinamide or guanidoacetic acid with another related dye, for in these experiments the extent of the gross cirrhosis was increased without increasing the rate of tumor formation.[240] The quantity and the type of fa added to the diets containing the carcinogenic dyes profoundly alter the rate o tumor induction. The multiplicity of confusing results have been reviewed by Miller and Miller[241] whose own investigations hav aided greatly in resolving the apparently conflicting results. Their findings[242] and those of others[187, 239] have now shown tha the effects of various levels of different fat or detergents on the rate of tumor formatio induced by feeding azo dyes can be explained by the amount of riboflavin maintained *within* the liver under these variou dietary conditions. The inhibitory effect o riboflavin on tumors induced by a dietar deficiency of choline has been mentione already and may indicate that there is final common pathway involved in the production of both types of liver cancer.

Little has been said here of liver tumo induced by agents other than the azo dye although references to hepatic cancers produced by other toxins are included in Tab 3. Sarcomata in rats' livers have been produced with methylcholanthrene and benz pyrene,[88] and reticulum-cell tumors of live have been found in rats treated with trypa blue.[114]

The prevalence of both cirrhosis and li cancer in human populations that occupy t "protein-poor" parts of the world tempts t experimentalist to transfer some of the abo findings into clinical terms. There appea to be little reason to doubt that dietary fa tors must play an important role in the common forms of disease in Africa, India and perhaps other regions.

HORMONES AND HEPATIC INJURY

In the foregoing discussion of the effect of diet on the production of experimental hepatic injury, either alone or in conjunction with hepatotoxic agents, emphasis was given in several places to the importance of the caloric intake of the animal. Almost every hormone of the body probably can be said to influence either the food intake or the caloric utilization of the animal, and to this extent at least they will affect correspondingly the results of experiments in which the incidence and the severity of various types of injury to the liver are being studied. In many investigations, conducted by clinicians and experimentalists alike, the influence of hormone therapy or deprivation on the food intake or utilization by the animal has not been fully understood when interpreting the possible effects of hormones on the development of hepatic injury. Pair-feeding and close observation of body weights of animals during the course of the experimental period cannot be overemphasized in this type of experiment.

In the early portion of the chapter reference has been made already to the effect of insulin deficiency on the liver. The fatty liver which rapidly develops in the depancreatized dog is corrected within a very short period by adequate treatment with insulin. Dietary lipotropic agents have no influence on the deposition of liver fat in diabetic dogs or alloxanized rats. The distribution of the fat in insulin deficiency appears to be in the peripheral (periportal) portions of the liver lobule,[158] whereas in choline deficiency both the fatty and the fibrotic lesions, as already noted, are initially nonportal. The periportal distributions of fat in diabetes (uncomplicated by lipotropic deficiency) and in the liver of the starved animals are in accord with the concept that regards the diabetic state as "starvation in the midst of plenty."

In 1935 Best and Campbell[23] reported that administration of an extract of anterior pituitary gland to dogs resulted in an increase in liver fat. As in starvation and diabetes, the distribution of the fat is periportal.[29] This effect of anterior pituitary extract has been confirmed by other investigators[216, 253] in rats and rabbits, and it has been shown that choline administration does not influence the amount or the distribution of the abnormal fat. Starvation and simultaneous injection of the anterior pituitary fraction into rats produces a greater degree of fat accumulation in the liver than does either procedure alone. These experiments indicated that the increase of fat in the liver is accompanied by a decrease in total body fat.[24] The increase in liver fat is inhibited partially but not completely by large doses of insulin given with comparably small doses of the pituitary fraction.[60] It appears that the effect of the pituitary extract is due to growth hormone, to ACTH, to an unidentified principle or to some combination of all these substances.[29, 205]

Chaikoff and his associates at Berkeley have published a series of papers on the effects of hypophysectomy on the livers of dogs. Hypophysectomy alone does not influence the fat content of the liver of the dog (up to 32 months); thyroidectomy alone in dogs fed a high-protein diet results in fatty livers; and in *both* hypophysectomized and thyroidectomized (HT) dogs, fatty livers appear earlier and are more severe.[94] Development of fatty livers in the latter animals (HT) fed a high-protein diet can be prevented by the daily administration of 2 Gm. of free choline chloride.[93] Previously, the authors had reported the development of cirrhosis in dogs deprived of both pituitary and thyroid glands,[65, 66] and this may be associated with the fat accumulation. However, they have also reported the presence of hepatic fibrosis in the persistently nonfatty liver of the hypophysectomized (only) dog,[64, 66] a finding in agreement with earlier reports of Graef, Negrin and Page,[122] although in their experiments coincidental hypothalamic injury was demonstrated in the animals. The nature of the cirrhosis that develops in the nonfatty liver of the hypophysectomized dog has not been elucidated further at the present time. It has been demonstrated recently[13] that in the dog hypophysectomy does not retard the regeneration of liver after partial hepatectomy, an effect that can be shown in the rat. In the latter species inhibition of hepatic regeneration following hypophysectomy is regarded as secondary to reduced food intake. The hypophysectomized dogs ate normally. Recently, injection of growth hormone into intact rats has been shown to intensify the effects of choline deficiency independently of any effect on food intake.[145]

Administration of cortisone[298] or hydrocortisone[145] decreases the severity of renal lesions and liver fat in choline-deficient rats. These hormones also ameliorate the lesions in hepatic necrosis produced by dietary means in rats.[293] The findings do not appear to be altogether in agreement with earlier observations[215, 300] that adrenalectomy in male rats and hypophysectomy in both sexes affords partial protection to animals on a diet low in lipotropic factors. However, weight loss, particularly in the hypophysectomized animals, could have been responsible for the lowering of the liver fat; alteration in intestinal absorption in the adrenalectomized animals could be another factor. More recently it has been found that rats treated with adrenocorticotropin and fed diets high in carbohydrate accumulate sufficiently large amounts of fat in the liver to impair some of its functions.[14] Also, it has been reported still more recently that focal and diffuse centrolobular necrosis with fatty degeneration develops in rats treated with desoxycorticosterone and salt administration.[303]

The sex hormones exert an appreciable influence on the response of rats to hypolipotropic diets. Castration in the male has little demonstrable effect, but ovariectomy is followed by an increase in liver fat.[300] György et al. have investigated the effect of estrogenic hormones in a series of experiments[136, 138, 301] and succeeded in demonstrating a definite lipotropic effect due to these hormones. More recently, Emerson et al.[89] have found that testosterone propionate aggravates both the renal and the hepatic lesions in choline-deficient female rats and the liver lesions in males. Once cirrhosis is established, there is considerable evidence of both a clinical and an experimental nature that atrophy of the reproductive system develops in the male. It has been demonstrated in the rat by Feiner and others,[102] using carbon tetrachloride.

Thyroidectomy has been shown to exert an influence on the degree of hepatic injury produced by a variety of means. Crystalline thyroxin injected into rats increases their susceptibility to liver damage due to chloroform administration.[230] Goitrogenic substances were found by György et al.[187] to prevent the development of experimenta dietary cirrhosis in rats. Earlier, this same group of investigators had found that thyroid ectomy exerted a similar effect.[300] In the same year, 1948, Handler[149] confirmed these findings in thyroidectomized and thiouracil-fed rats maintained on hypolipotropic diets. Thyroid feeding was found to result in a slight decrease in fat in the livers of both control and choline-deficient rats. A pro nounced decrease in the cholesterol concen tration in the livers of both groups of animals was observed to follow thyroid administra tion. Some of these effects of thyroxin may be influenced by not only the caloric demand of the animal but also the absorption of ingested food. Desiccated thyroid greatly acce erates the appearance of dietary hepatic ne crosis,[5, 149, 231] and administration of eithe propylthiouracil or potassium thiocyanat prolongs the length of time required for deat to occur from hepatic necrosis of dietar origin.[231]

EXPERIMENTAL HEPATIC INJURY PRODUCED BY SURGICAL MEANS

The classical method employed wherev possible to study the functions of an org is to remove it and then observe the sta of the surviving animal. Removal of the liv in mammals is peculiarly difficult, owing its intimate relation to the inferior vena ca and the necessity of providing a pathway venous portal blood to the heart. Seve satisfactory methods, usually employing 2 more operations at intervals of several da have now been devised, using dogs;[125,] they consist essentially of modifications the technic first devised by F. C. Mann of Mayo Clinic.[221] Recently, Markowitz has viewed and described these and other me ods of experimental surgery of the liver Technics for total hepatectomy in the have been developed also.[69, 275]

Simple excision of from one fifth to th

quarters of the liver is followed by restoration of the organ to its normal size within 6 or 7 weeks in dogs and 30 days in rats.[87, 106, 267] Early studies were concerned chiefly with the rate of restoration of liver mass and the manner in which the new tissue formed.[106, 172, 222] Replacement of the amputated liver lobes does not actually occur; instead, hypertrophy of the remaining lobes by cellular and lobular hyperplasia brings the total mass of the liver back to preoperative levels.[150] The influences of variations in the proportions of dietary fat, carbohydrate and protein on rate of liver regeneration in rats following partial hepatectomy have been studied in considerable detail by Vars and his colleagues.[126, 127, 318] They have found that fatty change in the regenerating remnant is not significantly above normal if adequate amounts of lipotropic factors are present in the diet. When animals were partially depleted of protein and maintained on low-protein or even nonprotein diets, liver protein was regenerated at a low but constant rate. Higher levels of dietary protein in the postoperative diet were associated with comparable increases in the amount of regenerated protein in the liver. The degree of increase depended on the quality, as well as the quantity, of the dietary protein. Gelatin and zein had little better effect than nonprotein diets, while beef, fibrin and whole-egg protein were associated with a greater amount of hepatic protein regeneration than was found even with casein at the same dietary level. The effects of low-choline diets or others low in cystine and methionine, as well as deficiencies of other food factors and vitamins, have been tested on regenerating hepatic remnants,[81, 203, 330] and in general the results are similar to those in intact animals. A number of investigations have confirmed the original findings of Rous and Larimore[283] that an important factor in hepatic restoration after partial resection is the relatively increased blood supply to the remnant. A patent bile duct is essential for restoration of the remnant.[284]

EXPERIMENTAL HEPATIC COMA

Acute hepatic failure can be produced by injection of hepatotoxic substances, but rarely do these fail to produce lesions of varying importance in other organs as well. Partial or total hepatectomy may result in death from liver failure, but many of the symptoms of hepatic coma in man cannot be demonstrated by this means in the animal. Rappaport and his co-workers[272, 273] have succeeded in inducing in dogs the experimental counterpart of clinical hepatic coma by a 3-stage operation. The first stage consists of ligation of the common hepatic artery and the formation of a partial Eck fistula.[111, 225] In later stages all named branches of the hepatic artery and the portal vein going to the liver are either ligated or have their blood flow diverted from the organ, which then survives in part on collateral circulation alone.[269] This technic became possible in the dog only after it had been discovered previously in Toronto that death (which otherwise always supervenes in the dog) after ligation of the hepatic artery could be prevented by postoperative treatment with antibiotics.[111, 225] Following completion of all stages of the operation, dogs that survive the last postoperative interval develop typical hepatic coma lasting up to 7 days. Examination of the livers of animals sacrificed or dying in hepatic coma revealed widespread hepatic necrosis with survival of only periportal shells of relatively normal parenchyma. Bile duct mucosa was unaffected. Rappaport et al. have studied the histology of these animals' livers and other organs not only in the acute phase of coma but also during the weeks of recovery when the liver gradually regenerates as the collateral circulation becomes more efficient.[274] One result of these studies has been the development of a new concept concerning the anatomic structure of the smallest functional hepatic unit.[271] Rappaport has also developed a technic for guided catheterization and roentgenography of the abdominal vessels.[270] He has applied the new method to the problem of studying the hepatic venous channels in animals subjected to various experimental procedures.[268]

Technics for producing obstruction of the bile duct and biliary cirrhosis were developed many years ago and have been reviewed by Markowitz.[224] There are excellent methods of producing biliary fistulae for the purpose of studying the external secretions of the liver.[309] Wachstein and Zak, applying these methods to dogs, have found an alteration in the histochemical distribution of alkaline phosphatase after experimental biliary obstruction.[321] Colwell[71, 72] has adapted the methods of producing biliary fistulae in dogs to the rat by inserting into the animal's abdominal cavity an artificial gallbladder of glass that leads to the exterior. Applying this technic to choline-deficient rats, he was able to demonstrate that accumulation of even large amounts of fat in the liver produced little detectable alteration in the quantity and the quality of the bile.

In conclusion, it might be emphasized that the study of hepatic disease in experimental animals fed deficient diets of various kinds has provided the experimental pathologist with an unparalleled opportunity to make detailed pathogenic studies of a number of lesions in animals that closely resemble those frequently encountered in man. Development of dietary cirrhosis and choline-deficiency induced hepatomata follows a course not unlike the natural history of these conditions in patients. Not all the problems of experimental pathology and physiology posed by the experimental lesions have yet been solved. Results of continued studies in these areas should provide information of interest and value to all who are concerned with the prevention and the treatment of human liver disease.

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Chapter 5

LIVER FUNCTION TESTS

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The known functions of the liver are so numerous that the number of possible liver function tests is also very large. It is not ntended in this chapter to consider every proposed test, but rather to limit the discussion to those of established clinical value, with special reference to the question of nterpretation. Two general points are becoming increasingly clear from recent work. First, no one test can be considered as a reliable index of function under all conditions. Second, the number of tests performed on one patient needs to be restricted to a small "battery" of tests, choosing those most appropriate to the clinical condition. For routine clinical purposes it is desirable to choose tests the results of which can be nterpreted on the basis of past experience, and it is more important to know a few tests well than to seek an indefinite multiplication of procedures.

CLASSIFICATION OF TESTS

The most important tests may be classified as follows:

1. Tests depending mainly on biliary excretion
    - A. Serum bilirubin
    - B. Bile pigments in urine and feces
    - C. Dye excretion tests
2. Tests mainly independent of biliary excretion
    - A. Serum proteins
    - B. Prothrombin response to vitamin K
    - C. Hippuric acid
    - D. Serum cholesterol
    - E. Galactose tolerance
    - F. Blood and urine amino acids
    - G. Plasma fibrinogen
3. Empirical tests
    - A. Serum alkaline phosphatase
    - B. Flocculation tests
    - C. Serum cholinesterase

A few generalizations may be made on the above classification. Thus, tests in the first group are of limited usefulness in the presence of jaundice. It is fairly obvious that a jaundiced patient probably has some disturbance of bile excretion, and refinements in the measurements of this are not always of value. Nevertheless, the serum bilirubin estimation is important as providing an accurate record of the intensity of the jaundice, and the direct and indirect estimations will assist in distinguishing hemolytic jaundice from the other varieties. In nonjaundiced patients, on the other hand, these excretory tests are of particular value, and the demonstration of latent jaundice, urobilinuria, or bromsulphthalein retention makes an important contribution to the diagnosis of cirrhosis and of preicteric hepatitis.

The second group of tests are rather more important in prognosis than in diagnosis, as the functions of the liver concerned in them tend to be depressed equally by a large variety of hepatic insults, so that the findings in, for example, hepatitis and obstructive jaundice may be very similar with tests such as hippuric acid and galactose tolerance. However, the serum protein estimation is also useful in the diagnosis of cirrhosis, and the prothrombin response to vitamin K and the cholesterol estimations are of some value in distinguishing surgical from medical jaundice.

The empirical tests are of particular value in differential diagnosis and have been developed mainly from this angle. They are among the most useful laboratory procedures valuable for distinguishing obstructive from nonobstructive jaundice.

INDICATIONS FOR LIVER FUNCTION TESTS

With any laboratory test it is of the greatest importance that it be quite clear exactly what question is being asked of the test; otherwise, the results may well be of little value. This implies a careful selection of patients suffering from conditions which are likely to be illuminated by the tests undertaken. The following is a list of such conditions which are suggested as a reasonable basis for discussion:

1. **Suspected Primary Liver Disease.** This is usually a case of possible hepatitis or cirrhosis, and jaundice may or may not be present. A wider range of tests is available in the absence of jaundice, but in general there is no difficulty in demonstrating any liver damage which may be present in these cases.

2. **Suspected Involvement of the Liver in Other Diseases.** Liver function tests have played an important role in the demonstration of hepatic pathology in conditions such as heart failure, hyperthyroidism, malaria, infectious mononucleosis and rheumatoid arthritis.

3. **Differential Diagnosis of Hepatic enlargement.** Here we are concerned frequently with conditions such as cirrhosis and carcinomatosis of the liver, and in these two the functional changes are typically quite different. However, changes similar to those in carcinomatosis are seen also in liver abscess and amyloidosis.

4. **Differential Diagnosis of Jaundice.** Hemolytic jaundice is easily distinguishable functionally from the other varieties, but great difficulty may be experienced in deciding between obstructive and hepatogenous jaundice. Many liver function tests are not helpful in this connection, but a number will give useful indications in a proportion of cases.

5. **Prognosis.** Many tests appear to have prognostic value, although the evidence supporting such claims has not always been very strong.

6. **Investigation of Anemias.** The contribution of liver function tests in this field has been mainly in the detection of excessive hemolysis. Pigmentary tests serve here as a confirmation of hematologic methods, or alternatively they may indicate the need for hematologic investigation.

The various tests will be considered below on the basis of their contribution to the types of case outlined above.

LIMITATIONS OF TESTS

It may be desirable to conclude this introduction by considering certain general criticisms of liver function tests (Ivy and Roth[69] Himsworth[62]; Hoffbauer, Rames and Meinert[64]) which continue to appear in the literature. These employ two main lines of argument. The first, which now is advanced less frequently, is that the reserve power of the liver is so great that only premortal changes in function are to be expected. The second is that changes in function occur in so many different conditions that their presence is of no value in diagnosis. It will be seen that the two arguments are somewhat contradictory

The first argument relied mainly on the evidence of hepatectomy experiments in dogs (Mann[108]) and is not difficult to counter With modern methods the frequency of frankly abnormal liver function in apparently healthy subjects with cirrhosis or convalescent hepatitis, for example, is well recognized. The second has more substance, and it must be freely admitted that absolute diagnostic deductions cannot always be drawn from these tests. However, the same might be said of findings such as albuminuria or hypertension, and yet we would hardly be prepared to neglect such observations.

The fact is that the only unequivocal clinical signs of liver damage are jaundice and possibly certain rather rare phenomena such as spider naevi and the aminelike odor occurring in severe liver failure (Watson[166]) Therefore, we are entirely dependent on liver function tests to demonstrate the presence of other functional disturbances of the liver which may be of great clinical significance. Thus in jaundice the types of disturbance are often characteristically diverse in the different varieties, and in the absence of jaundice the tests are even more important in diag-osis and prognosis. Of course, difficulties in nterpretation will be encountered, but these can be reduced to a minimum by a careful selection of patients and tests. Now the various tests indicated will be considered ndividually.

TESTS DEPENDING MAINLY ON BILIARY EXCRETION

Serum Bilirubin Estimation

This is an important basic observation which should be made in every case of liver damage that is investigated. It gives an accurate record of the intensity of any jaundice which may be present and may give some indication as to the type of jaundice.

The enormous literature that has developed on this subject since the pioneer observations of van den Bergh and Muller[8] in 1916 with the Ehrlich diazo reagent has been reviewed recently by Lemberg and Legge[86] and by Gray.[45] The original distinction between the direct and the indirect reactions has become overlaid with a multitude of varying technics, and with a genuine doubt as to whether two forms of bilirubin do in fact exist, as claimed by Fowweather,[39] Griffiths and Kaye[51] and others, or whether the wo types of reaction represent differences in physical state or in the nature of the bilirubin-protein bond (Watson[32, 167]). The latest contributions appear to indicate that there are ndeed two types of pigment concerned, but hat the direct pigment is not bilirubin at all (Cole and Lathe,[22] Najjar and Childs[118]). In the following account the terms "direct" and "indirect" are used in their usual arbitrary sense and refer to color intensities under various experimental conditions. They are not intended to indicate acceptance of he existence of two chemically distinct pigments, a proposition which requires further onfirmation.

The technical complications of the van den Bergh reaction are concerned mainly with wo aspects of the test. One of these is the hoice of a medium for the "indirect" or more correctly the "total" reaction. The original ethanol has been modified by the addition of ammonium sulfate to ensure complete protein precipitation (Haslewood and King[58]). Its use in this way has been criticized, since precipitation of the protein leads to loss of bilirubin, and various other media which avoid this disadvantage have been used. These include 50 per cent methanol (Malloy and Evelyn[107]), urea, glycerol and other agents.[26, 70, 124, 132, 167]

The second variable factor has been the time chosen for reading the direct reaction, which has varied from 30 minutes to 1 minute. Most of these methods have been concerned with the quantitative estimation of the two varieties of bilirubin with photoelectric instruments, and of recent years the tendency has been to discard the old qualitative procedures. The disadvantage of these was the extreme difficulty of defining exactly what was meant by direct, indirect and biphasic reaction, which depended too much on personal opinion.

So far as the "total" bilirubin is concerned the technics referred to above are more or less equivalent, but the interpretation of the proportion of direct pigment varies considerably with different methods. It is proposed in the present account to describe the results obtained with the technic of Malloy and Evelyn[107] as modified by Gray,[44] in which the direct pigment is read photoelectrically after 30 minutes and the total pigment is read in 50 per cent methanol solution also at 30 minutes. The indirect bilirubin is obtained by the difference between the total and the direct pigments. With this method one estimates direct and indirect bilirubin as separate entities, and the distinction between the two varieties has at least some clinical value. To avoid theoretical implications Gray refers to these results as the "direct-indirect quotient."

Normal values may be taken as from 0 to 1 mg. per 100 ml. for the total serum bilirubin, and most of this is indirect. A zone of latent jaundice exists from 1 to 3 mg. per 100 ml. In jaundiced subjects it is useful to note whether the direct or the indirect pigment predominates. In hemolytic jaundice more than half the pigment is usually indirect unless modified by secondary liver damage from anemia or by biliary obstruction from pigment stones. A preponderance of indirect pigment was not seen in any type of jaundice other than hemolytic. On the other hand, if more than half is direct the jaundice is probably obstructive or hepatogenous in origin.

Earlier claims to distinguish obstructive jaundice from the toxic and infective variety by the van den Bergh reaction have not been maintained, and it seems likely that these claims perhaps depended upon the greater average intensity of jaundice in biliary obstruction as opposed to the jaundice of hepatitis; the apparent proportion of direct pigment tends to rise with the level of total bilirubin in both groups, particularly with visual technics (Gray and Whidborne[47]). It is generally agreed that there is no *qualitative* difference between the results of the test in obstructive and in hepatogenous jaundice.

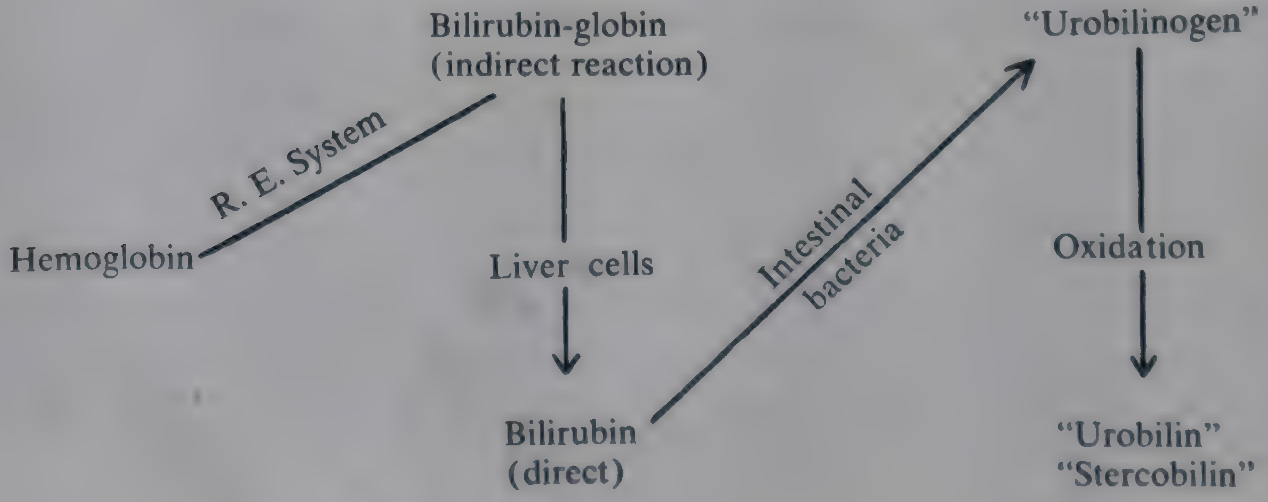
It remains to discuss the significance of the "direct 1 minute" bilirubin of Watson.[167] A number of workers have been impressed with the value of this test (Pollock[127]) in the diagnosis of cirrhosis and of preicteric hepatitis. The amount of pigment giving a direct reaction at 1 minute is said to be normally less than 0.2 mg./100 ml., and values above this may be significant even with a normal total bilirubin. Such values are also said to correlate with the appearance of bilirubin in the urine. The weakness of this procedure, however, lies in the inaccuracy of the measurement. This arises because the optical density corresponding to 0.2 mg./100 ml. with the usual dilution technic is only about 0.01; the ordinary photoelectric colorimeter cannot be used accurately in this range.

The *icterus index* of Meulengracht[115] is an approximate procedure which should not be regarded as a substitute for the more nearly accurate serum bilirubin estimation unless adequate laboratory facilities are lacking. The serum is compared with a 0.01 per cent solution of potassium dichromate, the index representing the number of times which th serum must be diluted in order to match th standard. The normal values are from 4 t 6 units, and the high levels in jaundice ru roughly parallel with the bilirubin conten However, carotin, and at times, hemolysis may interfere with the test, which is not recommended for general use. Greater accurac is obtainable if the serum is first percipitate with acetone[121] and then compared with th standard at a wave length of 460 μ,[60] but th procedure is then little less laborious tha the bilirubin estimation.

BILE PIGMENTS IN URINE AND FECES

Urobilin and Urobilinogen in Urine. Thes terms probably represent a group of substances rather than single chemical individuals but are adequate for the present purpose Urobilinogen is produced mainly by bacterial action on bilirubin in the small intestine It is partially reabsorbed into the portal circulation being re-excreted by the liver in th bile; the remainder is changed further t stercobilin, the normal stool pigment. Excessive hemolysis causes an increase in th amount of bilirubin reaching the gut an hence usually leads to high stercobilin excretion. These relationships are illustrate in Table 4. However, it should be note here that recent isotope studies by Londo et al.[90] and by Gray, Neuberger and Sneath[4] have shown conclusively that there is another source of stool and urine urobilinoge that does not depend on hemolysis. Glycin labeled with N^{15} was fed to patients wit porphyria, and the N^{15} content of hemoglobin and of the bile pigments was followe over a period. While most of the N^{15} exces

TABLE 4. BILE PIGMENT METABOLISM



n the urobilin group occurred after about 100 days, indicating its origin from hemoglobin synthesized in the early part of the experiment, up to 20 per cent occurred during he first few days and cannot have originated n this way. This dual source of the bile pigments does not appear at present to alter very much the interpretation previously placed upon their variations. Nevertheless, we should recognize the possibility of a nonhemolytic origin of urobilin in conditions such as pernicious anemia.

Urobilin and urobilinogen are of equal clinical significance and the choice of tests for qualitative work is a matter of convenence. Fresh urine specimens contain mainly he colorless urobilinogen which is converted slowly to the brown urobilin on standing; but his change can be accelerated by the oxidation with iodine followed by the spectroscopic examination for urobilin, or by the Schlesnger test with zinc acetate. Alternatively, a fresh specimen may be tested for urobilinogen with Ehrlich's aldehyde reagent, preferably followed by saturated sodium acetate. For quantitative estimation it is best to estimate urobilinogen by Watson's[144, 172] method, in which any urobilin present is reduced with ferrous hydroxide to urobilinogen which is then extracted with petroleum ether and estimated colorimetrically. For fresh specimens the process may be simplified by the direct addition of Ehrlich's reagent to the urine. The results may be given either as approximate Ehrlich units per 2 hrs., normally from 0 to 1, or as mg./24 hrs., normally 0 to 3.

Urobilinogen is found mainly in afternoon and night urine; therefore, morning specimens should be avoided for this test. In view of the bilirubin-urobilin cycle referred to above it is evident that the optimal conditions n urobilinuria are that some bile should reach the intestine and that some impairment of the excretory function of the liver should be present. Thus it is found particularly in hepatitis of moderate grades of severity, in partial biliary obstruction, and in cases of iver damage without jaundice. It may be completely absent from the urine, either in complete biliary obstruction or in severe hepatitis where secretion of bile is absent. In such cases a return of urobilinuria may herald improvement of function or relief of obstruction. It is said that this acholic phase in hepatitis rarely lasts longer than one week. In hemolytic jaundice urobilinuria may also be absent, but frequently occurs if any complication such as gross anemia is present.

It will be seen from this that in the presence of jaundice the significance of urobilinuria may be difficult to interpret, and the test is of greatest value in nonjaundiced patients, being particularly useful in cirrhosis. In preicteric hepatitis it also frequently occurs, but it should be remembered that any acute febrile disturbances can cause sufficient disturbance of liver function to give some urobilinuria, which can occur in other conditions not primarily hepatic, such as heart failure, severe anemias and following coronary thrombosis. Therefore, this finding is not such a specific indication of primary liver disease as is bilirubinuria; nevertheless, it is a valuable test for routine application.

Bile Pigments in Feces. The brown pigments normally coloring the stool are now recognized to be a mixture of several substances. Nevertheless, for clinical purposes "stercobilin" can be reduced to "stercobilinogen," which is estimated by methods identical with those given above for urobilinogen. The result usually is expressed as "fecal urobilinogen," giving normal values of from 40 to 280 mg. per 24 hrs.,[165] or from 30 to 220 mg. per 100 Gm. of stool,[99] according to the method used. Watson[165] has made an extensive study of this test, laying particular stress on the distinction between the results in malignant biliary obstruction (0 to 0.3 mg. per 24 hrs.) as opposed to those seen in gallstone obstruction (from 0 to 50 mg.). Although the values overlap, figures below 5 mg. are certainly suggestive of malignant obstruction, and figures above 5 in a case of obstructive jaundice favor a diagnosis of gallstones. This aspect of the test does not appear to have found very general application, perhaps because frequently laparotomy is indicated in both conditions irrespective of the results of the test.

A greater use for this procedure is probably in the detection or the confirmation of excessive hemolysis. While the stools discussed above always will be pale in color, the stool in hemolytic conditions is not abnormally colored, and the increased excretion of pigment can be detected only by chemical analysis. Watson's figures in hemolytic jaundice ranged from 300 to 2,500 mg. per day, and very gross increases in the concentration of pigment are also commonly found, up to 2,000 mg. per 100 Gm. of stool.[99] The test is equally useful in detecting hemolysis in the absence of jaundice and gives high results not only in the hemolytic anemias but also in pernicious anemia and in conditions such as malaria, after incompatible blood transfusion, and after fractures of the long bones.

There are some limitations to the test as an indication of hemolysis. Thus, falsely low values may result from constipation, while in the recovery stage of hepatitis or biliary obstruction high results may be seen for periods of a few days, since the excretion of bile pigment by the liver may be temporarily excessive under these conditions.

Coproporphyrin in Urine. The occurrence of increased amounts of urinary coproporphyrin in cases of liver disease is an old observation going back to the work of Garrod[41] in 1892. The significance and the usefulness of the finding have been explored further in recent years, particularly by Watson and his colleagues,[169] and by Rimington[135] and others.

The exact details of the metabolism of coproporphyrin are not completely known, but it seems clear that it is synthesized, in common with other porphyrins, mainly in the bone marrow from simple precursors such as glycine. After circulating in the blood it is secreted by the liver into the bile, and any failure of this process is reflected in increased urinary excretion. It has been shown by isotope studies,[46, 90] in which glycine labeled with N^{15} was fed to patients with porphyria, that most of the urinary coproporphyrin is associated with hemoglobin synthesis and not with hemolysis. It apparently arises as a by-product of hemoglobin manufacture, and it may be noted that the variety normally excreted, Type I, is structurally different from hemoglobin (Type III) and therefore could not arise by hemolysis. In certain liver diseases, however, Type III coproporphyrin is also excreted, and the origin of this is not

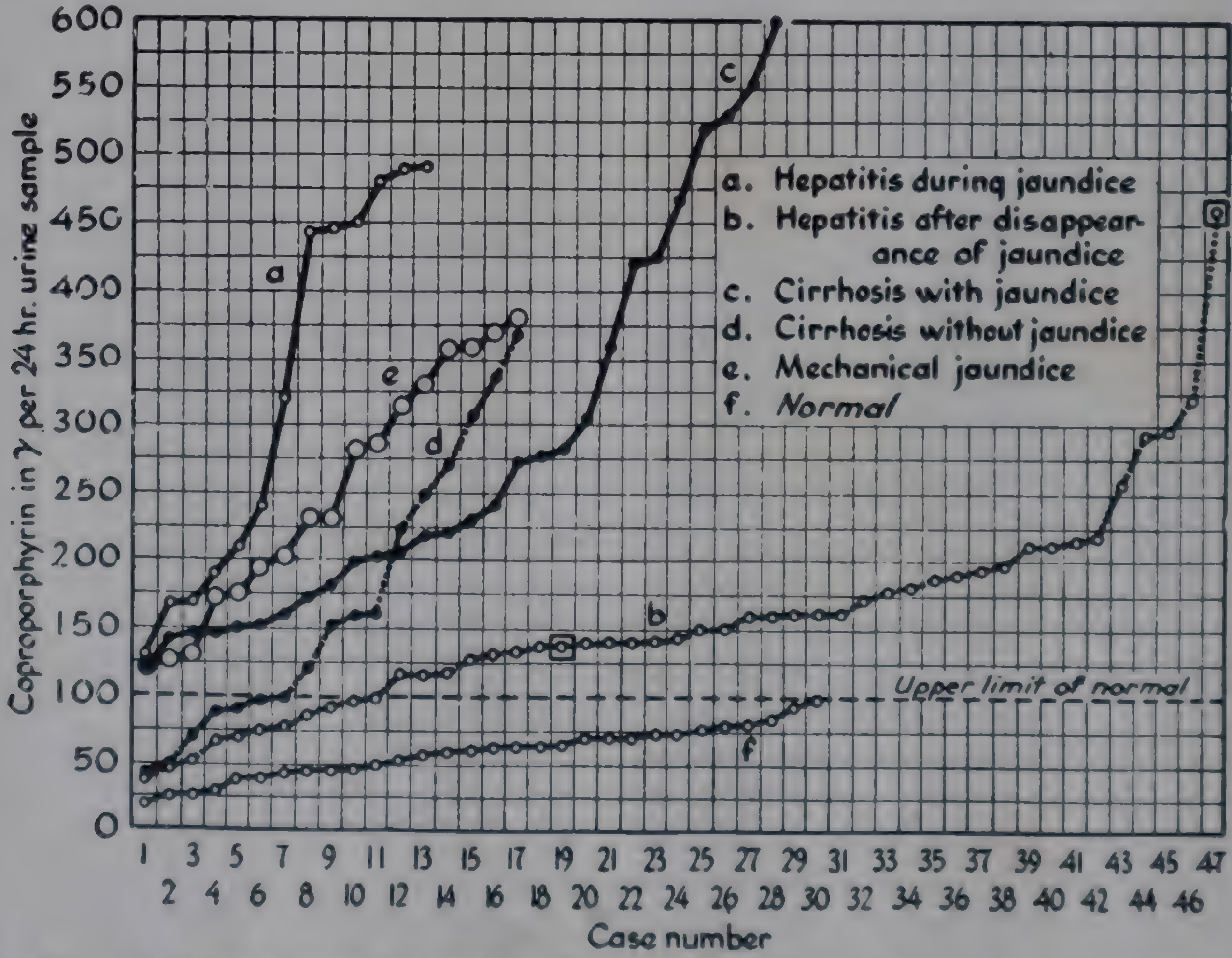


FIG. 34. Urine coproporphyrin in hepatitis and cirrhosis. NOTE: According to Dr. C. J. Watson, the results have been found to be too low, and the values are therefore relative rather than absolute. (Watson, C. J., and Larson, E. A.: Physiol. Rev. **27**:478)

definitely known. It will be seen that there are certain analogies here with the metabolism of urobilinogen, and in spite of notable differences excretion of the two compounds tends to run roughly parallel in many cases. However, coproporphyrin excretion is a more constant finding in liver damage than urobilinuria, since its appearance does not depend upon the presence of bile in the intestine.

The method of estimation is technically more difficult than that of urobilin, requiring a sensitive photoelectric fluorimeter. The urine when fresh contains certain porphyrin precursors, and various means of converting these to porphyrin have been suggested. Watson's[143] latest method gives values in normal subjects up to 160 μg. per 24 hrs. The test can also be done on a 2-hour afternoon specimen, when the normal limits extend up to 20 μg. per 2 hrs.[27]

Increased excretion is found in all varieties of liver damage, and values up to 3 or 4 times the normal are seen frequently. Although not dependent on the presence of jaundice, the values in hepatitis and in cirrhosis are on the whole higher in patients with jaundice than in those without, a small proportion of the latter falling within the normal range. These features are illustrated by some of Watson's[169] earlier results illustrated in Fig. 34. The method of estimation employed here gave a lower range of values to those now accepted, but the clinical relationships are unaltered. It will be seen that the test is of no value in the differential diagnosis of jaundice, as the results are about equally abnormal in the obstructive and the hepatogenous varieties. The excretion in hemolytic jaundice is variable, but considerable increases may be found at times, probably in proportion to the attendant hepatocellular damage. Excessive coproporphyrinuria is not an entirely specific indication of primary liver disease, as it occurs also in many fevers and infections, in blood diseases, in poisoning by alcohol, sulfonamides and heavy metals and in the porphyrias. The excretion of coproporphyrin is also diminished below normal by drugs such as amithiozone.[185] Of course, in some of these conditions the increase may reflect the presence of secondary liver damage, but in the porphyrias and the anemias a more general metabolic derangement appears to be more probable. It will be seen that the results are somewhat similar, in a qualitative way, to those of the urobilinogen test except in the case of obstructive jaundice.

In addition to this work on total urinary coproporphyrin, much work has also been done on the nature of the isomer excreted. Normal subjects excrete Type I coproporphyrin, and this isomer is also the one principally found in hepatitis, infections, blood diseases and in many cases of cirrhosis. However, in alcoholic cirrhosis, in poliomyelitis, and after various drugs such as alcohol, lead and sulfonamides, the Type III coproporphyrin is the principal variety found.[169] This interesting difference led Schwartz et al.[143] to develop a simple method of analysis depending on differential solubility of the two isomers which is capable of routine application. The difference between the results in alcoholic cirrhosis, as opposed to cirrhosis following hepatitis, is particularly striking and deserves further attention by workers in this field.

In concluding this section the condition known as idiopathic coproporphyrinuria should be mentioned, as it may lead to occasional difficulty in interpretation. This is a rare clinical entity described by Watson et al.[173] in which quite large amounts of Type III coproporphyrin are excreted without any abnormal symptomatology. The individuals are quite healthy and have not had any family history of the disease, nor any drug history. Although evidently analogous to the porphyrias, this appears to be a benign condition with good prognosis.

Bile Salts. The familiar Hay's test with flowers of sulfur is a traditional procedure which is still widely followed. In spite of the introduction of more elaborate quantitative methods of estimation by Lichtman[88] and others, no practical alternative to Hay's test for routine work has been advanced. The test is reasonably sensitive, concentrations down to 0.5 mg. per 100 ml. of sodium taurocholate or less being detectable, but is not entirely specific. The significance of positive results does not appear to have been analyzed in detail, but such findings are typically found in obstructive or hepatogenous jaundice. However, in long-standing jaundice the reaction may become negative, and occasionally it may be positive in the absence of jaundice. Perhaps more critical appraisal of this time-honored test is needed.

DYE EXCRETION TESTS

A number of dyes, among which we may include bilirubin and stercobilin for convenience, are excreted in the bile and can be used to test the excretory function of the liver. These include Azorubin S, Rose Bengal, phenoltetra-chlorphthalein, and the more popular bromsulphthalein (phenoltetrabromphenolphthalein disulphonate). Only the use of bilirubin and bromsulphthalein will be considered here.

Bilirubin Tolerance Test. This theoretically attractive test, introduced by von Bergmann[9] and by Eilbott[34] in 1927, is performed by injecting intravenously a dose of bilirubin of 1 mg. per kg. body weight and estimating the percentage retained in the blood after 4 hours. A total dose of 70 mg. should not be exceeded. The compound is rather expensive and not very easy to dissolve, the most innocuous medium being 0.1 M sodium carbonate. Normal subjects show up to 5 per cent retention at 4 hours.

The test is of most value in the absence of jaundice and has been used effectively by Kornberg[83] to reveal the existence of residual liver damage for long periods after infective hepatitis. In addition to practical difficulties, certain theoretical objections have been advanced by various workers, and the test has been largely superceded by the more popular bromsulphthalein test.

Stercobilin Tolerance Test. Similar remarks apply to Watson's[164] stercobilin tolerance test, which might well be used more generally if a suitable preparation of stercobilin came on the market.

Bromsulphthalein Test (B.S.P.). The use of this convenient dye was introduced by Macdonald[92] in 1938, and since then numerous modifications of technic have been made by the originator[93] and by others. The most important change has been to increase the dosage, the generally accepted technic being to inject the dye in a dosage of 5 mg. per kg. body weight and to determine the percentage retention in the blood at 45 minutes (Mateer et al.[110]). Normally, no more than a trace remains at this time. Alternatively, blood may be collected at 30 minutes, when retentions up to 10 per cent are allowable.

This test appears to approach nearer than any to the perfect function test, although it must be remembered that only one function is being tested. It possesses both the advantages and the drawbacks of a pure function test. The results are abnormal in a high proportion of cases of liver damage of all types, including hepatic cirrhosis, heart failure, etc. The mechanical effects of biliary obstruction also naturally produce retention, and therefore the test is of no value in the differential diagnosis of jaundice. Indeed, it is doubtful whether it is worth doing in jaundiced patients who can be assumed to have impaired excretory function anyway. Various formulae have been introduced relating the degree of dye retention to the bilirubin level in jaundice with the object of overcoming this objection,[186] but they do not appear to have found general acceptance.

It is one of the tests of choice for the demonstration of liver damage in nonjaundiced patients and probably gives a higher percentage of positive results in cirrhosis than any other single test. It is also the test that becomes positive earliest in experimental human infective hepatitis,[120] but it is hardly suitable as a diagnostic test in patients with acute illness suspected of having hepatitis. Its very sensitivity may lead to some difficulty in interpretation, since temporary functional disturbances often give rise to significant degrees of retention. Such findings have been noted in fevers and infections,[82] in anemias, in shock,[24] following operations, and in such chronic debilitating diseases as rheumatoid arthritis[27, 137] and diabetes mellitus.[187]

Perhaps the theoretical basis of the test is not quite so simple as has been indicated. Thus, clearance from the blood is much more rapid than excretion in the bile,[16] suggesting that the dye must be stored before excretion, perhaps in the Kupffer cells.[81] Furthermore, B.S.P. still leaves the blood, although at a reduced rate, in the absence of the liver.[19] However, in spite of these facts there is no doubt as to the usefulness of the test, both clinically and in experimental studies of liver damage.[18]

TESTS MAINLY INDEPENDENT OF BILIARY EXCRETION

SERUM PROTEIN ESTIMATIONS

Some of the most important functions of ne liver are connected with protein metabo- sm, such as the deamination of amino acids nd the maintenance of the normal blood evel of albumin, globulin and fibrinogen. In ne present section we are concerned with ne concentrations of albumin and of the arious types of serum globulin. While none f the changes found is an entirely specific ndication of liver damage, the combination f low albumin with high globulin is very ypical of generalized liver disease. The re- ults of the classical salting-out procedures vill be discussed first. Of these the Howe[65] odium sulfate method is the most popular, ollowed by nitrogen estimations by the Kjeldahl method. Other fractionating agents uch as sodium sulfite and methanol have een used also.

The normal serum albumin level as de- ermined by sodium sulfate fractionation is rom 4 to 5.5 Gm. per 100 ml., and the ver disease is one of the important causes f a fall in serum albumin, the fall presum- bly being due to a direct failure in synthe- is. This is not an early change and therefore s found more often in chronic conditions uch as cirrhosis or subacute hepatitis rather han in acute hepatitis. When found it is im- ortant both from its relation to symptoma- ology and to prognosis. Thus values below .5 Gm. per 100 ml. correlate fairly con- tantly with an obstinate edema, which is ssociated with the attendant fall in colloid smotic pressure of the plasma. The globulin raction also contributes significantly to the olloid osmotic pressure in hepatitis, and ccording to Iversen[68] the best correlation vith edema and ascites is obtained by use f the formula:

$$3.5 \times \text{albumin} + \text{globulin} = 14.2$$

n his series, patients with values for this unction below 14.2 always had edema. This ormula is not unlike the earlier one of Govaerts,[43] which has found similar applica- ion to the edema of nephritis. In prognosis gures below 2 Gm. per 100 ml. usually indi- ate severe irrecoverable liver damage and a poor outlook, as shown by the work of Witts[61] and his colleagues.

Apart from liver disease, low albumin values are also found in nephritis, and in many forms of malnutrition, using this word in its widest sense to cover all causes of a negative protein balance. This would include the semistarvation of famine conditions, deficient absorption of protein in diseases of the pancreas, the stomach, or the esophagus, and loss of protein from ulcerating surfaces as in burns, ulcerative colitis, etc. In some of these conditions an element of liver damage may also be present, but the main factor is a lack of available protein rather than a deficiency of production. Therefore, hypoalbuminemia is a finding that needs to be interpreted with due regard to the rest of the clinical picture.

The serum globulin level is normally from 1.5 to 3 Gm. per 100 ml., and raised values are typical of hepatitis and cirrhosis. The rise may occur at any stage of these diseases but in hepatitis is more marked in the subacute or chronic stages. The finding is very helpful diagnostically in this type of case but has no direct relation to prognosis nor to symptomatology with rare exceptions. These exceptions were certain cases of cryoglobulinemia due to hepatitis, in which the tendency of the globulins to come out of solution on chilling was so marked as to produce Raynaud phenomena in the hands and the feet on exposure to cold.[30, 170]

Liver disease is one of the most frequent causes of hyperglobulinemia but is by no means the only one. Other conditions to be remembered include acute infections, particularly of virus or protozoal origin, such as lymphogranuloma, glandular fever and kala-azar, chronic infections such as subacute bacterial endocarditis, osteomyelitis, syphilis and tuberculosis, and a number of diseases of the bone marrow and of the reticuloendothelial system. The most prominent of these is multiple myelomatosis (plasmacytoma), but smaller elevations also can occur in leukemia, Hodgkins disease, and with multiple skeletal metastases.

These two changes have a striking effect on the serum *albumin globulin* (A/G) ratio (normal from 1.5 to 2.5), and this method of expressing the results has become very popular in clinical literature. The effect of the changes discussed above will be to lower this, and some workers prefer to report total protein and A/G ratio in place of the separate albumin and globulin levels. In the writer's opinion this is undesirable, as the fall in albumin and the rise in globulin are largely independent of one another, and it is more important to know the absolute levels. If one knows these accurately, the calculation of the ratio does not add anything significant to existing information. This certainly applies to prognosis, where the albumin figure alone is significant, and to a lesser degree to diagnosis. These points are illustrated in the protein figures on 3 typical cases of chronic hepatitis given below. The correlation of symptomatology with albumin level is evident in these cases, which also show the variability of the total serum protein in hepatitis.

While the cause of the fall in albumin in liver disease is fairly clear, we have no exact knowledge as to why the globulin rises. Since the rise is particularly prominent in subacute and chronic hepatitis and in cholangitis but may be absent in purely degenerative conditions such as chloroform poisoning, the suggestion is that it represents a reaction to some irritant such as a pyogenic organism or the virus of infective hepatitis. This reaction presumably is aroused in the Kupffer cells of the liver and may well extend to other parts of the reticuloendothelial system. Such a hy
pothesis would suggest that the hyperglobu
linemia of cirrhosis is to be regarded as th
terminal stage of an infective condition
however, the lack of any published evidenc
on this point does not encourage any furthe
speculation at the present time.

The discussion so far has been limited t
the results obtained by salting-out technics
However, the *electrophoretic* technic ha
been much used of recent years and now
must be considered. This method of frac
tionation depends upon movement of th
charged protein particles in an electric fiel
and is technically more difficult than salting
out methods. The original Tiselius[156, 15
apparatus was somewhat elaborate and no
well suited to clinical application, but th
recent development of paper electrophore
sis[33, 38, 180] has changed the situation, and thi
method has become a routine procedure i
some laboratories. It has the advantage
requiring very small amounts of material, fo
total protein estimation plus electrophoresi
can easily be carried out on 0.2 ml. of serum
On the other hand, the results are not ver
easy to make quantitative, and this aspect o
the technic is still under investigation.

In all these methods the serum protein
are separated into 4 main fractions: albumin
α, β and γ globulin. The albumin moves mos
rapidly at the reaction usually employe
(pH 8 to 8.6), and the gamma globulin i

TABLE 5 A. SERUM PROTEINS IN CHRONIC HEPATITIS
(Gm. per 100 ml.)

	CASE 1 *Ambulant, mild jaundice*	CASE 2 *Ill, some edema*	CASE 3 *Bedridden, gross edema and ascite*
Albumin (Normal 4 to 5.5)	4.2	2.1	1.5
Globulin (Normal 1.5 to 3)	5.5	5.2	3.5
Total protein (Normal 6 to 8)	**9.7**	**7.3**	5.0

TABLE 5 B. ELECTROPHORETIC SERUM ANALYSIS

	TOTAL PROTEIN	PER CENT OF TOTAL PROTEIN AS			
		Albumin	α	β	γ
Normal Limits	6–8	55–65	9–14	7–15	6–1
Typical Hepatitis Serum	7.2	50.2	4.4	20.0	25.
Typical Cirrhotic Serum	5.2	35.3	9.8	15.2	39.

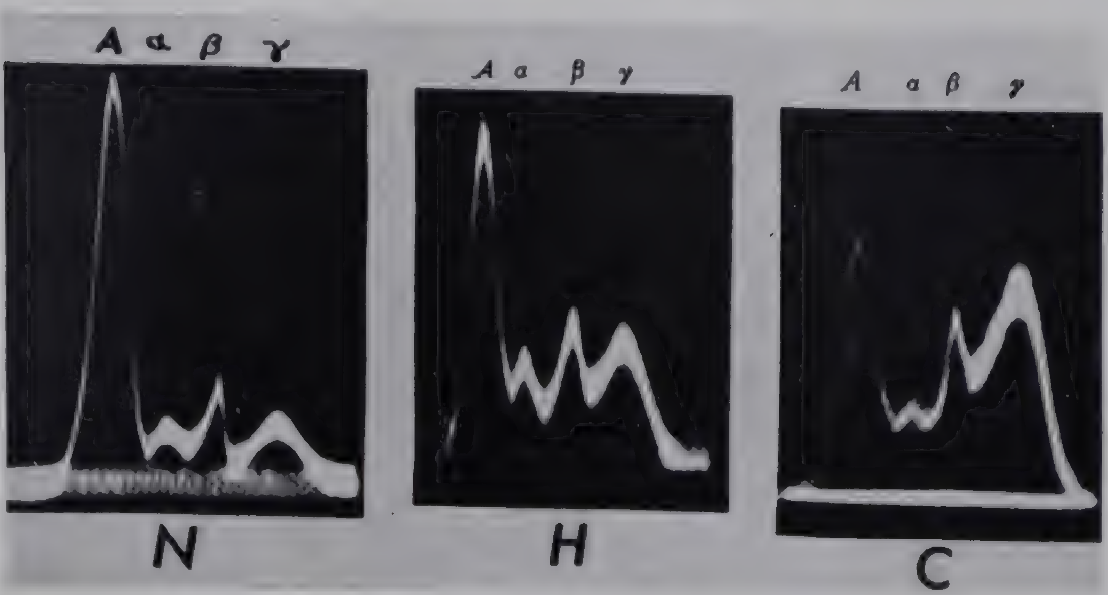


Fig. 35. Electro- horetic diagrams of ormal serum (N), epatitis serum (H) nd cirrhotic serum C). Descending oundary. (Wuhrmann, F., and Wun- erly, C.: Die luteiweisskörper es Menschen. Basel, chwabe)

he slowest. So far as albumin is concerned he results are very similar to those obtained y salting out, but more information is obained about the globulin fraction; in liver isease the main increase usually occurs in he gamma fraction, which is, of course, also he fraction mainly increased in infections nd is the principal carrier of antibodies. The esults usually are given in terms of total rotein and in percentages relating to the ndividual fractions. Typical results of an lectrophoretic analysis of pathologic serum re shown in Table 5 B.

Frequently, the results are expressed raphically or by an optical device known s the Schlieren diagram, as shown in Figure 5, which illustrates the same two cases Wuhrmann and Wunderly[182]).

With paper electrophoresis similar results re obtained, but are usually presented as hotographs of the stained paper in conjuncion with a total serum protein figure; as hown in Figure 36. From this data it is sually possible to say that the pattern is ither normal or abnormal in a characteristic ashion, but the observation lacks precision. number of suggested quantitative methods ased on paper electrophoresis are on trial.

The interpretation of electrophoretic data s not yet completely standardized but so far s liver disease is concerned follows much he same lines as those already outlined bove under salting-out methods. The typical indings are still low albumin with high globlin figures, the globulin being mainly amma globulin. The main difference lies in reater detail available about the globulin raction, which is helpful at times in eliminating other forms of hyperglobulinemia, such as the high β globulin of nephritis or the distinctive types of globulin often seen in myelomatosis.[7, 73, 182] So far as the ordinary routine diagnosis and prognosis of straightforward hepatic disease is concerned, it is doubtful whether electrophoresis presents any substantial advantage over salting-out methods.

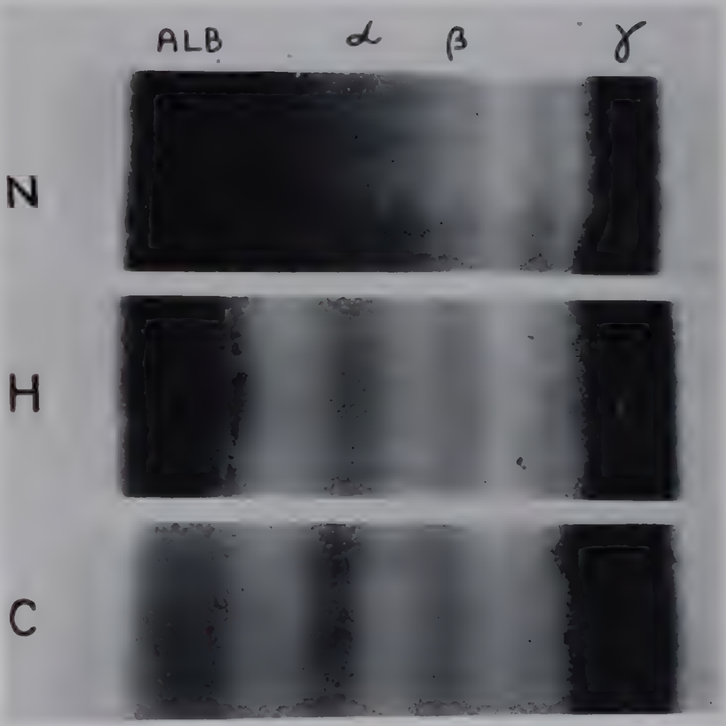


Fig. 36. Paper electrophoresis of serum proteins in normal subject (N), hepatitis (H) and cirrhosis (C). (From Dr. F. V. Flynn)

Electrophoresis has been of great importance in relation to the flocculation tests of liver function. On the whole, these tests have more affinity with electrophoretic analysis than with salting-out procedures and may be used with advantage as an adjunct to either method. They may be regarded very broadly as a short cut to the demonstration of increased gamma globulin in the serum, although this statement is an oversimplification of the position. This subject is discussed further in a later section.

PROTHROMBIN RESPONSE TO VITAMIN K

The theoretical basis of this test is shown in Table 6. This is a simplified scheme that ignores certain recent developments in the field of blood clotting which are not relevant to the test. It will be seen that prothrombin is manufactured from an unknown precursor in the liver under the influence of vitamin K. It is estimated by Quick's method,[129] which consists in adding an excess of calcium ions and of thrombokinase to the oxalated plasma, when the clotting time is decided almost entirely by the prothrombin content. Normal plasma under these conditions clots in something under 20 seconds, and longer "prothrombin clotting times" represent a deficiency that can be expressed on a percentage basis.

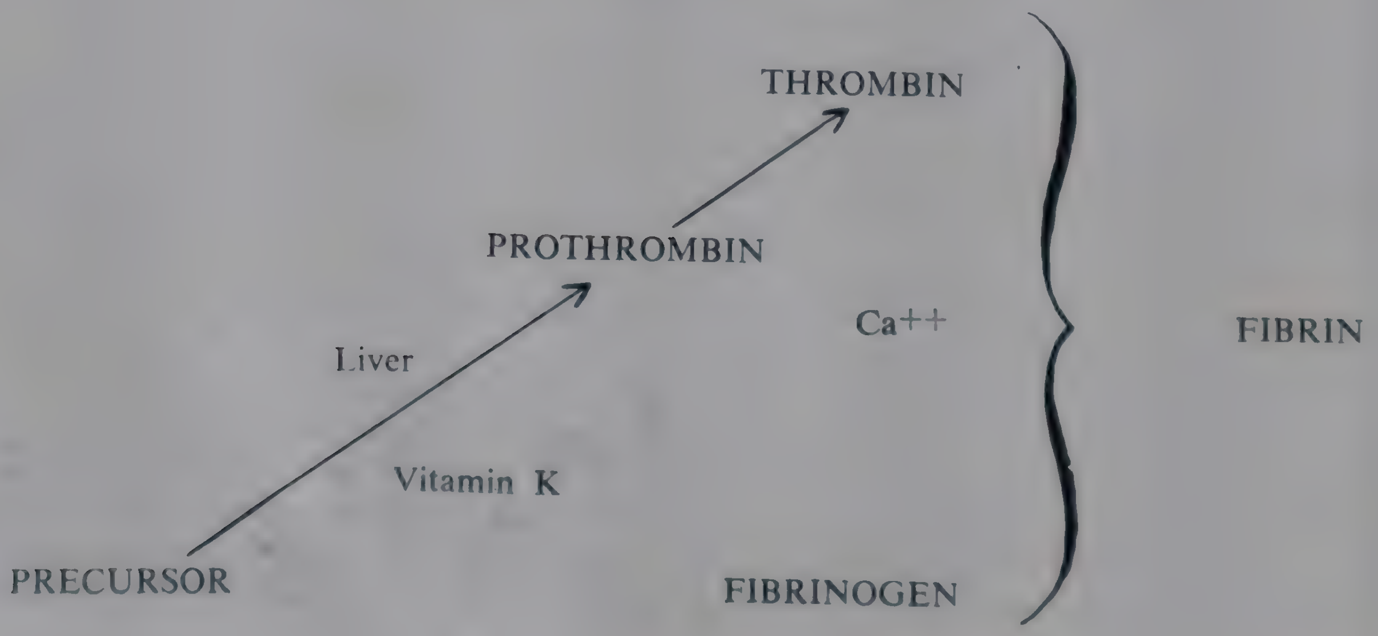
Low plasma prothrombin can occur in liver disease from two causes. First, the liver may be so damaged as to be unable to synthesize prothrombin, even if presented with all the appropriate materials. Second, supplies of vitamin K may be withdrawn, owing to absence of bile from the intestine; it has been established that vitamin K requires bile for its proper absorption from the gut. Of course, both these abnormalities may coexist.

It follows from this that in order to us prothrombin estimations to test liver function, it is first necessary for the patient t exhibit a low plasma prothrombin level Given this, then the test is conducted b administering vitamin K in the form o 76 mg. of "synkavite" by the intravenou route.[145] Then the prothrombin estimation i repeated after a suitable interval which ma be either 4 or 24 hours, and the state of live function is judged by the rise in the prothrombin level, if any. Failure to respon indicates poor liver function, and a rapi normalization suggests that the initial deficiency was due to lack of vitamin K rathe than to liver failure. While the test is more convincing if carried out as described, sometimes the first part is omitted, and the prothrombin estimation is not done until afte the vitamin K administration. Naturally, a low value under these conditions has the same significance as indicated above.[145, 153]

This test has been used mainly in jaundiced patients. It is particularly indicated i surgery is contemplated, since the risk o hemorrhage at operation with a low plasma prothrombin level is considerable. In this type of case a failure to respond usually means either that the jaundice is of hepatogenous origin or that biliary obstruction i complicated by very severe secondary damage. In either event the prognosis is poor and the operative risk is increased.

This test would be of considerably more value in the differential diagnosis if every

TABLE 6. PROTHROMBIN RESPONSE TO VITAMIN K



undiced patient had initially a low plasma
rothrombin level. Unfortunately, according
most authors only about one third of such
atients fulfill this criterion and therefore
ecome eligible for the test.[153] Unger and
hapiro[159] claimed a higher incidence of
ositive results, but their method was much
ore time-consuming, and it is not clear
hat proportion of their patients were jaun-
iced. In spite of these disadvantages, some
orm of prothrombin estimation is strongly
dicated in cases of surgical jaundice.

HIPPURIC ACID TEST

This convenient test, originated and de-
eloped by Quick,[128] depends upon the esti-
ation of urinary hippuric acid following the
dministration of sodium benzoate. The
eoretical basis of the test is not so simple
s might be supposed. Hippuric acid is
ormed by the conjugation of benzoic acid
nd glycine, and this conjugation takes place
ot only in the liver but also in other parts
f the body, such as the kidney and the
testine. The kidney also has the task of
xcreting the hippuric acid formed and thus
as important as the liver in this test. In
act, a similar procedure was once used by
ingsbury and Swanson[78] as a test of renal
unction. Therefore, its use as a test of liver
unction assumes that the kidneys are nor-
al. Granted this, if a sufficient dose of
enzoate is administered, the limiting proc-
ss in the formation of hippurate appears to
e the power of the liver to synthesize gly-
ine, and under these conditions the excre-
ion of hippuric acid gives a good indication
f the functional state of the liver.

Alternative technics are available. The
riginal one[128] employs an oral dose of 6
Gm. of sodium benzoate, when normal sub-
ects excrete over 3 Gm. of hippuric acid
(expressed as benzoic acid) during the suc-
eeding 4 hours. Later, Quick[130] introduced
is intravenous modification in which 1.77
Gm. of sodium benzoate is injected, and the
ormal excretion should exceed 0.7 Gm.
ver a 1-hour period. Some precaution
hould be taken to ensure that renal function
s adequate, such as the simultaneous per-
ormance of a urea clearance test, as advo-
ated by Sherlock.[148]

This test is of limited value in the differential diagnosis of jaundice, as equally low values are seen in hepatitis and in malignant biliary obstruction.[59] However, patients with gallstone obstruction give results much nearer to normal, provided that the obstruction is not too long standing; therefore, in a case of obstructive jaundice a normal test favors gallstones as a probable cause. Also, it has been much used prognostically in cases of surgical jaundice, particularly by Boyce and his colleagues.[13] Values below 2 Gm. by the oral method were held to indicate a poor prognosis and to constitute a partial contraindication to operation. It is probable that the prothrombin estimation has tended to supersede the hippuric acid test in this respect of recent years.

However, in nonjaundiced patients results of the greatest value have continued to accumulate, and the test is of undoubted value in this type of case.[28, 139, 150] It has been used in the diagnosis of cirrhosis, in the assessment of liver damage after hepatitis associated with arsenical treatment, and in the demonstration of liver involvement in conditions such as thyrotoxicosis, meningitis, rheumatoid arthritis, etc.[15, 113, 125]

It is perhaps a particularly appropriate procedure for the investigation of the so-called hepatorenal syndrome, since the renal factor here exerts a contributory influence, and some of the lowest results have been recorded in this condition.[12] A general correlation of the results with prognosis in a mixed group of medical and surgical cases was also established by Delor and Reinhart.[28]

It will be evident from the foregoing account that the hippuric acid test is of most value in prognosis and in quantitating the degree of liver damage in cases where the diagnosis has already been established. Therefore, it comes into the same class as the bromsulphthalein test, and if it should have diminished at all in popularity of recent years it is probably on account of the greater technical convenience of the B.S.P. test, which occupies a shorter time and involves fewer manipulations.

SERUM CHOLESTEROL ESTIMATIONS

The normal level of the serum cholesterol varies from 150 to 300 mg. per 100 ml., although occasional apparently normal subjects may exceed these limits. However, the percentage present in the ester form is more constant, being usually between 60 per cent and 80 per cent of the total. In liver disease alterations may occur both in the total cholesterol and in the ester ratio.

In spite of much work on the subject, going back almost 100 years, the exact pathologic basis of the test still appears to be in doubt. The rise of blood cholesterol in jaundice was demonstrated in 1862 by Flint[37] and the fall of ester cholesterol was recognized by Feigl[35] in 1918. Since then much work has been done by Gardner and Gainsborough,[40] Thannhauser[155] and others.[21, 151, 158] The principal accepted facts are as follows. Cholesterol is a major constituent of bile but is excreted also by the intestinal epithelium. Probably it is synthesized mainly in the liver, and enzymes that will esterify cholesterol are found in the blood and in liver extracts. Exclusion of bile from the intestine tends to raise the total blood cholesterol level without necessarily altering the ester ratio; however, this is not due to simple retention of the cholesterol normally excreted in the bile, since similar changes have been noted in cases of biliary fistula. Impaired hepatocellular function causes a fall in the ester cholesterol and thus may prevent the rise of total cholesterol which normally accompanies obstructive jaundice.

As a result of these factors the total cholesterol is usually above normal in uncomplicated biliary obstruction, and this finding is of some value in diagnosis. In such cases the cholesterol level tends to parallel that of bilirubin, and the ester ratio will be normal. A fall in this ratio during the course of the disease indicates the development of liver cell damage. In extreme cases the total cholesterol may fall below normal, a serious prognostic sign. In hepatitis the total cholesterol may be normal or moderately raised with some fall in the ester ratio. The ester ratio has normally been considered to be of value in the differential diagnosis of jaundice,[71, 178, 147, 176, 177] but recent work by Zieve[184] indicates that the fall in ester ratio is related more closely to the intensity of jaundice than to its cause.

In cirrhosis there is little change if the condition is well compensated. In severe cases, however, a fall in the total cholester with a very low ester ratio may be see which appears to represent the end result c gross liver failure from any cause and ind cates a poor prognosis.[88] Similar finding occur also in severe thyrotoxicosis, sever anemias and terminal cachectic states; it ma be that they depend on impaired liver func tion in these conditions, but this is unprovec

The estimation of total cholesterol wa formerly a very popular estimation in case of suspected cholelithiasis, on the hypothes that it reflected a general metabolic disturb ance with high blood and bile cholestero and hence a tendency to the formation c gallstones. Now it is recognized that thi theory was without foundation, as there i no simple relationship between the bloo and bile cholesterol values.[122] Any elevatio seen in such cases usually is due to biliar obstruction and is, of course, independent c the actual cause, being equally prominent i obstruction by tumors. However, such idea die hard, and a proportion of estimation probably are still undertaken on the basis c this discarded idea.

It should be mentioned here that hig cholesterol values are seen also in a numbe of diseases not directly connected with th liver, such as nephritis, diabetes mellitus an the Niemann-Pick syndrome. A small bu statistically significant rise is found also i pregnancy, the importance of which ha been somewhat exaggerated in the past i relation to theories of gallstone formation

It is evident that while very strikin changes in the blood cholesterol certainl occur in liver disease, it is not always eas to draw absolute conclusions from them The trend of values is said to be more sig nificant than single estimations. The simul taneous changes in free and ester cholestero present at times a puzzling picture, and i must be admitted that the end result in an severe liver failure is the same, i.e., lo levels for both the total cholesterol and th ester ratio. It is probable that prolonged ex perience with the test is necessary before it full implications are realized, but neverthe less it has been used widely both for diag nostic and prognostic purposes. It is possi ble that recent advances in the study of lipi metabolism[91] may clarify the situation an ead to an improvement in the present poition.

GALACTOSE TOLERANCE

A number of different sugars have been sed to test the glycogenic power of the ver, the principal ones being glucose, levuose and galactose. The last appears to have efinite advantages over the other two in one r more particulars. Thus in the case of lucose, although the frequency of lag storge types of curve in cases of liver disease is vell recognized and sometimes such results re of diagnostic value, glucose tolerance is ubject to the overriding control of the inulin mechanism, and obviously it is desirable to eliminate this variable if possible. Levulose is free from this objection, but its pecific estimation is more difficult than in he case of galactose, and after equivalent loses the blood levels reached are much ower. It was also shown in Mann's[108] hepaectomy experiments in dogs that animals vithout livers could utilize levulose to some xtent, while galactose was not metabolized, o that levulose must be removed from the blood partly by a nonhepatic mechanism.

The principle of the galactose test is simble. After administration of the sugar, the ate of conversion to liver glycogen is judged ither by the rate of removal from the blood or by the amount excreted in the urine. It s almost essential to use methods of estination which are specific for galactose, the isual procedure being to remove glucose by veast adsorption before estimating the residual sugar by any standard method. In the oral method 40 Gm. of sugar is given to the asting patient. The older procedure was hen to estimate the urinary total sugar over a 5-hour period, when less than 3 Gm. should be excreted.[6, 146] It is preferable, alhough also more laborious, to estimate the blood galactose levels[76, 94, 138, 175] at ½, 1, 1½ and 2 hrs. afterward, when the highest value should not exceed 80 mg. per 100 ml., and the sum of the 4 half hourly values, similarly expressed, should not exceed 160 (the galactose index).[94]

In this method the sugar reaches the liver by the portal vein, its normal physiologic oute. However, equally good results may be obtained by injecting 25 Gm. of galactose intravenously, when the blood galactose should have returned to normal after 2 hours (Althausen et al.,[1, 5] King and Aitken[76]). This method has the advantage of avoiding any difficulties in absorption in gastric or intestinal disease, for example, which at times may interfere with the oral method.

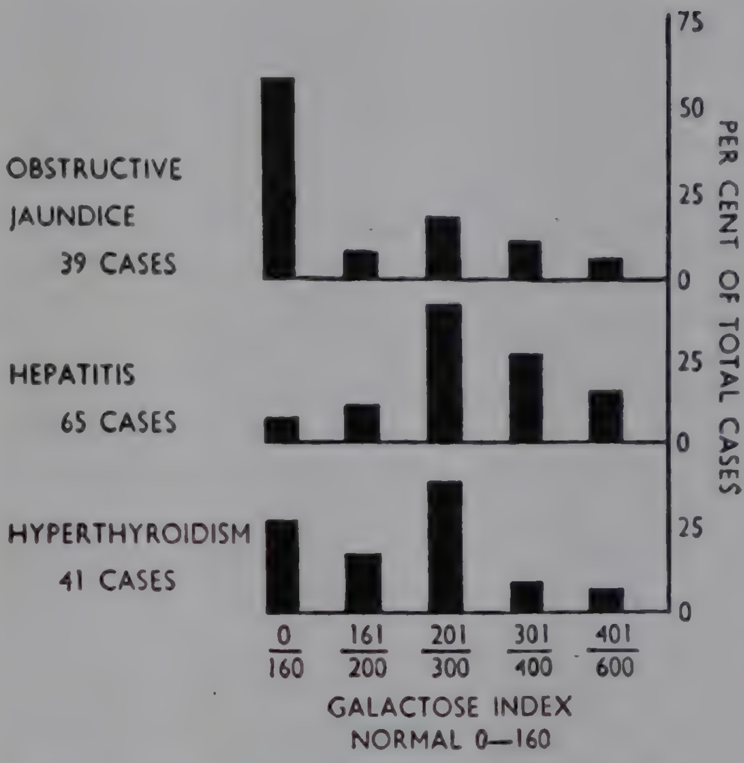


FIG. 37. Galactose index. (Maclagan, N. F.: Practitioner 162:200)

The results of the two methods run fairly parallel with certain exceptions to be noted below. Impairment of function is demonstrable in a high proportion of cases of hepatitis and cirrhosis. Most cases of early biliary obstruction give normal results; after 3 weeks, however, the liver damage resulting from obstruction becomes evident in an increasing proportion of cases as the duration of jaundice increases.[95, 145] Therefore, the test is of value in differential diagnosis if the condition is not too long standing. These findings are illustrated in Figure 37.

The test has also found considerable application in the demonstration of liver damage in other diseases and particularly in thyrotoxicosis, a condition in which the glycogenic function of the liver is affected particularly and in which up to 75 per cent of cases may give positive results (Althausen et al.,[1] Maclagan and Rundle[105]). It is a curious anomaly that this finding is obtained only with the oral modification of the test, the intravenous method giving mainly normal figures (Barnes and King[3]). This has been interpreted as indicating that increased intestinal absorption is the main cause of the high oral tests in thyrotoxicosis; against this is the fact that an attempt at the direct demonstration of increased galactose absorption in patients with this condition by Moseley and Chornock[117] gave negative results. There is also considerable collateral evidence of liver damage from morbid anatomic studies[4] and from the intravenous hippuric acid tests.[55]

It appears possible to the writer that perhaps the intravenous galactose test may be misleading in the special case of thyrotoxicosis, on account of the increased rapidity of circulation that is known to be present. This would result in the same sugar molecules being presented more often to the liver cells in a given time. This condition would not be quite the same with the oral test, where the major factor is presumably a failure of the liver to filter off the galactose when first presented to it by the portal blood. Whatever may be the explanation, the results of the oral test correlate better here with the other available evidence of the hepatic state in thyrotoxicosis. The test also runs reasonably well parallel with the clinical severity.[3, 105] No great claims have been made for its value in the management of the disease, but it has been found of some use in the diagnosis of borderline cases.

Thus galactose tolerance may be said to constitute a good all-round test of the glycogenic function of the liver, which has been found of value mainly in the differential diagnosis of jaundice and in thyrotoxicosis. It must be admitted, however, that since the test was developed better diagnostic methods for both these conditions have been developed, and perhaps the test is destined to become mainly of historic interest. However, it is of such great theoretical importance as to merit continued consideration for special problems.

Blood and Urine Amino Acids

One of the well-established functions of the liver is the formation of urea from amino acids by a process of deamination. However, this function is one which appears to carry considerable reserve, and demonstrable failure is rather uncommon. All the expecte results, which include high blood amino aci levels, low blood urea and aminoaciduria have been observed in a few cases of gros liver failure from causes such as acute atrophy, advanced cirrhosis, long-standing biliary obstruction,[36, 131, 141, 152] etc.

The frequency of *amino-aciduria* encountered varies with the technic employed. Th occurrence of leucine and tyrosine crystal in natural urine is an old observation i severe liver disease but is quite rare. If th urine is concentrated by evaporation, thes crystals may be seen more often, and Lichtman[88] has devised a special method of estimating tyrosine which demonstrated tha smaller increases in excretion were quite commonly seen in a variety of hepatic conditions not necessarily very severe. This abnormality is not confined to tyrosine, a shown by the more recent work of Dent and Walshe[29] who demonstrated by paper chromatography that a moderate rise in the excretion of many other amino acids could frequently be shown in infective hepatitis of moderate severity. They described 6 different patterns of abnormal urinary amino acid excretion characteristic of liver damage and were particularly impressed with the constancy of increased cystine excretion. This observation does not appear to have been followed up by other workers.

The blood changes referred to above are much more rare, but blood urea values down to zero and amino acid nitrogen levels up to 200 mg.[131] per 100 ml. (normal 4 to 8) have been recorded. After remaining of academic interest for many years, this aspect of liver function has become of greater importance recently, owing to the work of Walshe[160, 161] on hepatic coma. The biochemical changes in this condition never have been easy to reconcile with the clinical condition, and no one test has appeared to afford any obvious explanation of the comatose state. However, recently Walshe[160] has called attention to the constancy of disturbed blood amino acid pattern in the condition, and also to the increase in glutamine concentration in the cerebrospinal fluid that accompanies it. Later, he showed that treatment by administration of glutamic acid apeared to be of benefit in hepatic coma.[161] his particular amino acid was known preiously to have some effect on cerebral funcon, both experimentally and possibly in ertain cases of mental deficiency. The sugestion that it acts by lowering blood amonia appears to be unlikely in view of the ecent work of Schwartz et al.,[142] who found o direct correlation between coma and lood ammonia levels. Therefore, the mode f action of glutamic acid is not clear at the resent time, but these findings certainly epresent an important advance in the paology and the treatment of hepatic coma.

Plasma Fibrinogen Estimation

The normal plasma fibrinogen concentraon varies from 0.2 to 0.4 Gm. per 100 ml. nd it has been shown by animal experiients that fibrinogen is formed in the liver, s it falls to low levels after hepatectomy. n the other hand, it is usually raised in ny acute febrile illness. Hence, the values liver disease may be high, normal or occaonally low. In mild cases of hepatitis a ight rise is usual, but in more severe cases is rise may be abolished. Abnormally low alues in liver disease are restricted to cases f gross liver damage, such as acute yellow trophy and advanced cirrhosis, where figres as low as 50 mg. per 100 ml. may be een.[56, 149] Therefore, the estimation is of ttle diagnostic or prognostic value but reains an interesting finding of theoretical nportance.

EMPIRICAL TESTS

Serum Alkaline Phosphatase

The characterizations of this enzyme have een reviewed recently by King.[75] This is an nzyme that hydrolyzes organic phosphates ich as those of glucose or glycerol, yieldg inorganic phosphate and the organic adicle. It is most active at pH 9.5 but has ppreciable activity at blood reaction (pH .4). It may be determined by estimation f phosphate liberation from glycerol phoshate, giving normals from 0.5 to 4.0 Boansky[11] units, or by estimation of phenol berated from phenyl phosphate, giving noral limits of from 3 to 13 King-Armstrong nits.[77]

The serum alkaline phosphatase level is increased in a number of bone diseases, since the osteoblasts constitute one of its major sources in the body. This relationship was known for many years before the work of Roberts[136] in 1933 directed attention to the changes found in liver disease. This observation of the high values found in obstructive jaundice was followed quickly by the demonstration of high concentration of the enzyme in the bile of dogs by Armstrong, King and Harris,[2] who also showed that the level rose in the blood in experimental obstructive jaundice. Later, other workers have found raised values in hepatitis, cirrhosis, hepatic carcinomatosis, liver amyloidosis and abscess; however, the values in obstructive jaundice are on the average higher than those found in other liver conditions.[42, 53, 98 100, 148] The interpretation of results in relation to the liver naturally presupposes that the bones are not affected by any disease likely to raise the level, such as rickets, Paget's disease, osteogenic sarcoma, etc.

This test usually is included under the term "empirical" because the reason for the raised values in liver disease is not certainly known. Earlier theories included the simple retention of the enzyme because of failure of biliary excretion[2] and secondary effects on bone metabolism following the steatorrhea that usually accompanies obstructive or hepatogenous jaundice.[136] However, since quite high values are seen in the absence of jaundice, e.g., in cirrhosis, in liver abscess and with hepatic carcinomatosis, it appears more likely that the deranged liver cell secretes the enzyme into the circulation when damaged or irritated in certain ways. However, there is no obvious reason why some types of liver disease should cause this phenomenon while others do not. Thus, normal values are seen in a proportion of cases of hepatitis and cirrhosis and are usual in hemolytic jaundice and in purely degenerative conditions, such as chloroform poisoning.

It will be evident from the above facts that this test may be of value both in the presence of jaundice and in its absence. The findings in a series of cases collected by the writer are illustrated in Figure 38. It will be seen from this that in jaundice high values

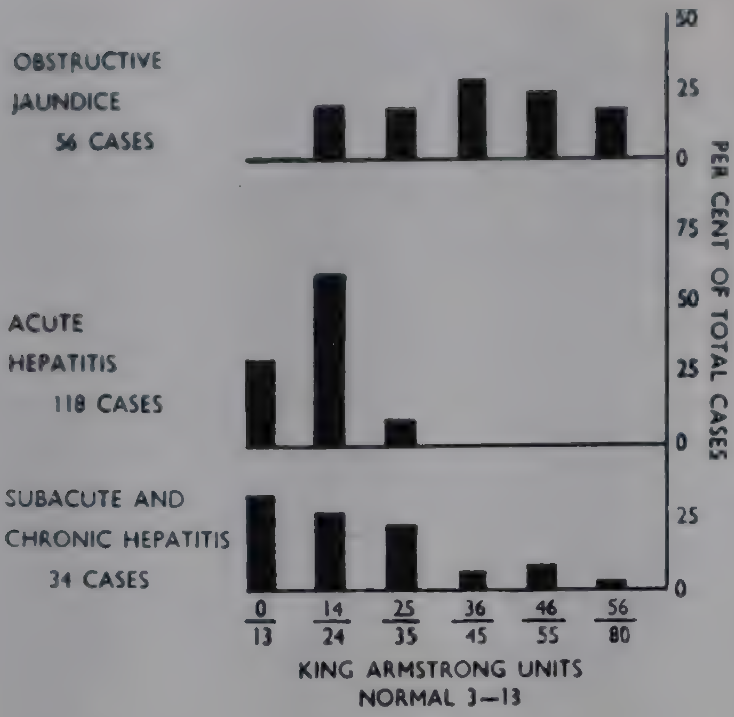


FIG. 38. Serum alkaline phosphatase. (Maclagan, N. F.: Practitioner **162**:200)

would favor a diagnosis of either obstructive or hepatogenous jaundice, and values over 35 units are suggestive of the former variety. Normal values are very uncommon in biliary obstruction and would make this diagnosis unlikely, although such a result is compatible with hepatitis. In the absence of jaundice the test is of value in confirming a diagnosis of carcinomatosis of the liver, a condition in which raised values are very frequent. High values may be seen also in cirrhosis, although less frequently.

The serum alkaline phospatase is thus an extremely useful indicator of vario types of liver disease, although it rea should not be called a liver function test it does not test any definitely known fur tion of the liver. It will be seen below th in many respects its tendencies are oppos to those of the flocculation tests, as a resi of which these two tests can be combined great advantage, as described in a lat section.

FLOCCULATION TESTS

Under this heading we may consider group of empirical tests, mainly elaborat as the result of some chance observatio which in spite of their dubious origins ha proved to be of considerable value in tl investigation of liver disease. The earlie appears to be the formol gel test develop by Napier[119] in 1921 as a test for kala-aza The next in chronologic order was tl Takata-Ara[154] reaction, originally design to distinguish lobar from broncho-pne monia, and later used as a diagnostic test f cirrhosis. Since then we have had the Wei mann coagulation band,[174] cephalin chole terol,[57] colloidal gold,[48, 96] thymol turbi ity,[97] colloidal red,[31, 106] cadmium sulfate, zinc sulfate[104] and ammonium sulfa tests.[66, 180] Some detail of these various tes is illustrated in Table 7.

It will be seen from this that all the tes exhibit a strong family resemblance, diffe ing mainly in the nature of the precipitati

TABLE 7. CHEMISTRY OF FLOCCULATION TESTS

TEST	PRECIPITATING AGENT	pH	IONIC STRENGTH	SERUM DILUTION FACTOR	PROTEIN FRACTION ACTIVE	
					Precipitating	*Inhibitory*
Takata-Ara	$HgCl_2$	ca 10	0.15	2–16	α, β, γ	Albumin
Formol gel	HCH:O	ca 8	0.15	1	α, β, γ	Albumin
Cephalin-cholesterol	CC Emulsion	ca 8	0.12	26	(α, β), γ	Albumin
$CdSO_4$	$CdSO_4$	ca 8	0.10	1	(α, β), γ	Albumin
Sharlach Red	Sharlach Red	ca 8	0.075	2–8	?	?
Weltmann	$CaCl_2$	ca 8	0.02–0.002	51	(α, β), γ	Albumin
Colloidal gold	Colloidal gold	7.8	0.01	61	γ	Albumin α,
Thymol	Thymol	7.8	0.01	61	γ (β)	Albumin
$ZnSO_4$	$ZnSO_4$	7.5	0.002	61	γ	—
$(NH_4)_2SO_4$	$(NH_4)_2SO_4$	5.5	4.8	51	γ	—

agent used and in the pH and the ionic rength of the medium. In all cases addi- on of the reagents to normal sera produces o effect, while with abnormal sera a pre- pitate, turbidity, or flocculation results.

In many cases the mechanism of the tests as quite unknown when they were elabo- ted but has become considerably clearer uring the last 10 years following the intro- uction of the electrophoretic technic. Nu- erous experiments with electrophoretically olated protein fractions from normal and epatitis serum have been carried out bv abat, Moore, Hanger and colleagues,[72, 116] laclagan and Bunn,[103] and others.[49, 123, 181] has been shown that the most significant ctive precipitating fraction is the gamma obulin. Normal albumin exerts an inhibi- ry effect, while hepatitis albumin is a much ss effective inhibitor. In the case of the ymol test, phospholipids are also an essen- al ingredient, and normally these are con- ibuted by the β globulin. However, this action alone produces no precipitation of e thymol reagent, so that its effect appears o be mainly that of a nonspecific phos- holipid donator.

No two of these tests are exactly alike in echanism. Thus the α and β globulins are hibitory for the gold test but are precipi- ted by the Takata reagent, although they have little influence on many of the other tests.

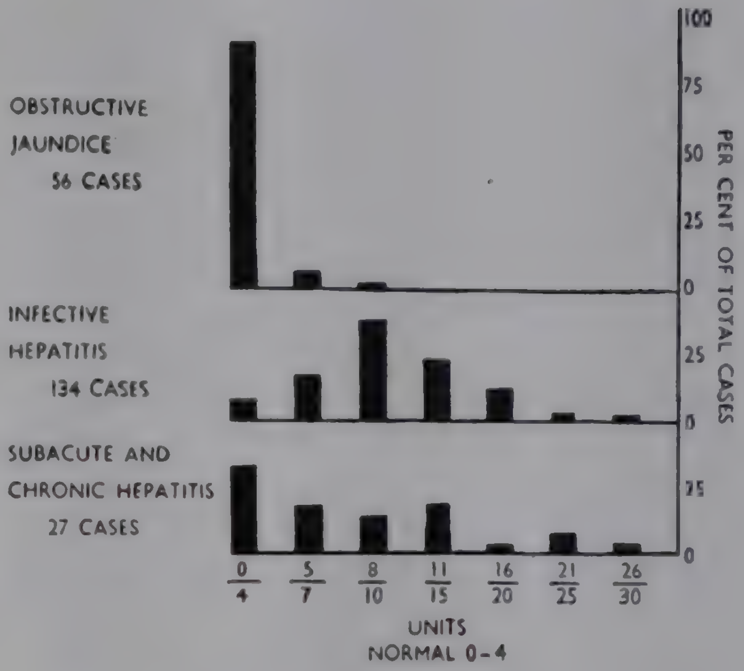


FIG. 39. Thymol turbidity test. (Maclagan, N. F.: Practitioner 162:200)

All these tests exhibit some correlation with the serum globulin level,[101] which is close in the case of the Formol gel test but very slight with others such as the thymol turbidity. The newer zinc sulfate and ammonium sulfate tests correlate fairly closely with the serum gamma globulin level, and the latter has been claimed as a gamma globulin estimation. However, it is probable

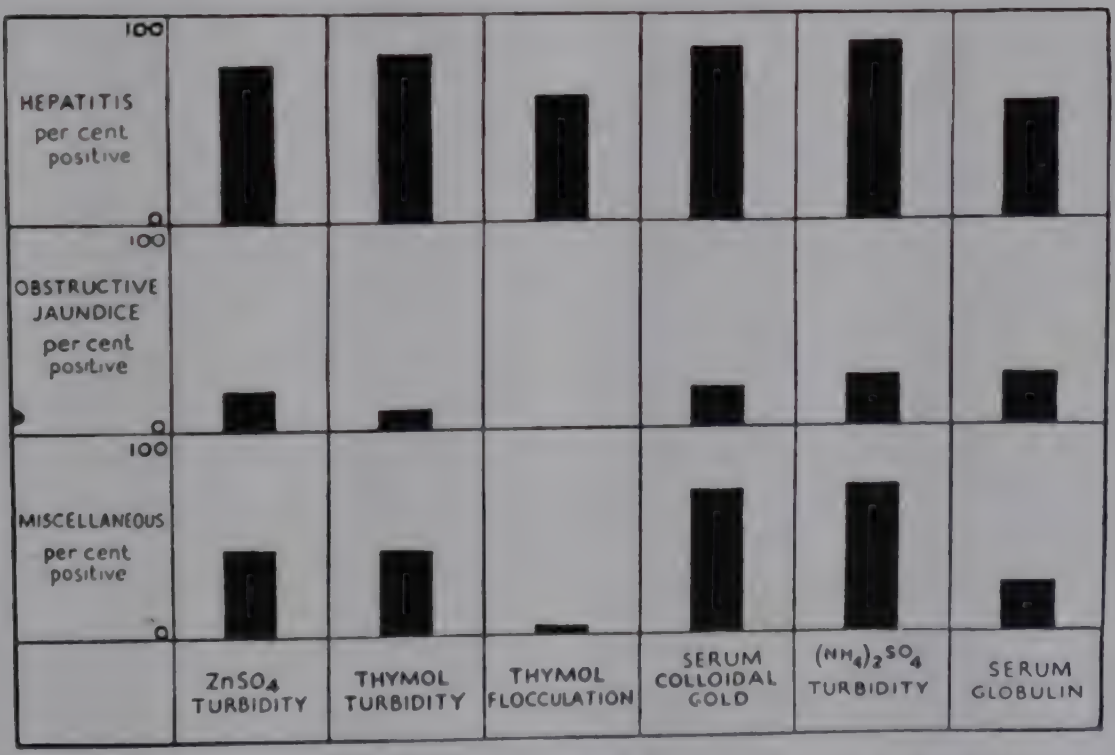


FIG. 40. Comparison of results with flocculation tests in liver disease. (Maclagan, N. F.: Ciba Foundation Symposium on Liver Disease 1951, p. 4, Churchill, London)

that thymol, gold, cephalin cholesterol and Takata-Ara tests depend as much on qualitative changes in serum albumin as on the globulin concentration. It may be agreed that the closer the dependence upon total globulin, the less valuable the test becomes, since the more accurate globulin estimation would be preferable to an approximate one. There is no doubt that most of these tests do give definite additional information over and above that obtainable from the globulin determination.

No two tests are exactly alike in their clinical results, although the colloidal gold and the colloidal red tests are very alike. It will be impossible to consider them all in detail, but certain salient features are illustrated in Figures 39 and 40. Figure 39 illustrates typical findings with the thymol turbidity test in a personal series of cases. It will be seen that the test is mainly negative in obstructive jaundice and mainly positive in jaundice due to hepatitis. The differences are sufficiently striking to be of value in differential diagnosis. In chronic hepatitis the variation in results is greater, but a high proportion of positive results is seen. Figure 40 shows a comparison of a number of those tests in a representative cross section of cases. It will be seen from this that the various tests vary considerably in sensitivity and in selectivity, the two qualities varying approximately inversely with one another; the thymol flocculation test was the most selective and therefore of most value in differential diagnosis of jaundice. Kunkel's zinc sulfate test appeared to be about the most sensitive but gave a fairly high proportion of "false positive" results in nonhepatic conditions.

None of these tests is, of course, strictly a liver function test, and none is an entirely specific indication of liver dysfunction, since the protein pattern responsible is common to a number of diseases. Thus, positive results may be seen in the following conditions:

Acute infections: Glandular fever, virus pneumonia.

Chronic infections: Tuberculosis, syphilis, subacute bacterial endocarditis, malaria, kala-azar

Miscellaneous: Rheumatoid arthritis, severe anemias (gross lipemia, thymol only)

In some of these such as glandular fever and malaria, genuine liver damage is certainly present. In the others this is more doubtful and is probably not the main cause of the positive results.

All this means that the tests must be used intelligently with due regard to the whole clinical picture and not interpreted blindly as though they were specific liver tests. With this proviso they will be of great value in the diagnosis of acute and chronic hepatitis and in the differential diagnosis of jaundice They are also useful in prognosis, being among the last tests to become negative following acute hepatitis. This was well shown by Neefe and Reinhold,[120] who found the thymol flocculation test positive up to 12 months after the onset in their series of cases of experimental human hepatitis. The reality of the residual liver pathology was shown by simultaneous liver biopsies.

The limitation of the tests lies in their lack of specificity and in the fact that they are not invariably positive in all cases of hepatitis.[10] Most workers have reported from 90 per cent to 95 per cent of positives in acute infective hepatitis, and a smaller percentage perhaps about 50 per cent, in cirrhosis. Postarsphenamine jaundice, which was principally syringe-transmitted serum hepatitis also only gave about 50 per cent of positive results. Similarly, the findings in obstructive jaundice vary with the individual tests. Thymol and gold are usually negative and practically never strongly positive in this condition, while the Takata-Ara reaction may be positive in up to 40 per cent of cases. Reports on the cephalin cholesterol test in obstructive jaundice have varied from 16 to 78 per cent of positives in differen series.[57, 79, 126]

Also, much work has been done on the correlation between individual tests. In liver disease, they have a general tendency toward correlation, and gross discrepancies are uncommon apart from those noted above in obstructive jaundice. Therefore, in any individual case of hepatitis the tests are likely to be either all positive or all negative.[102, 111, 17] However, the reverse is true of multiple myelomatosis where it frequently happens that one or more tests may be strongly positive while others are completely negative. This is valuable diagnostic pointer when seen.[104]

In view of all these complexities the choice f a test for routine application is a difficult nd rather personal matter. The writer's resent preference is for the thymol, the zinc ulfate and the gold tests. These 3 are similar echnically and employ conveniently small olumes of serum. The thymol test is particurly useful in hepatitis and in the differential iagnosis of jaundice, while the other 2 are erhaps more sensitive in cirrhosis and in onhepatic conditions, such as rheumatoid rthritis, etc. It is an advantage to do several f these tests if possible so that the dissociaion of myelomatosis can be demonstrated.

SERUM CHOLINESTERASE

The serum enzyme concerned here is the seudocholinesterase and should be distinuished from the true cholinesterase which s responsible for the transmission of the ervous impulse at cholinergic nerve endings. he function of pseudocholinesterase is obcure but it appears to be involved in protein etabolism.[85] It is associated chemically ith the α globulin fraction of the serum proeins.[74] Normal values vary considerably ccording to the method of estimation sed.[109, 112, 178]

In liver disease low values were first reorded by McArdle[112] in 1939, who conidered the test a sensitive indication of imaired function. Later work has not entirely onfirmed this, and the test does not appear o be of great value in the differential diagnois of jaundice.[109, 178] It has been claimed hat it gives an earlier indication of recovery n hepatitis than the flocculation tests.[178] The reatest interest in the test lies perhaps in its pparent relation to protein metabolism, as hown by its correlation with the serum albunin levels (Kunkel and Ward[85]). This relaionship is further exemplified by the low alues recorded in fatty liver disease in inants in the West Indies (Waterlow[163]). This ondition is characterized by very low serum rotein figures, and the serum cholinesterase vas one of the few functional tests to give bnormal results.

CHOICE OF TEST

It is generally agreed that no one test of liver function is appropriate to all cases, and it is usual to employ what has been called a "battery" of tests, which may be large or small according to individual preference. However, even with the restricted list of tests chosen for discussion here, it is hardly possible to do all of them on every patient, and it is necessary to make some selection. Considerable differences of opinion naturally exist on this question, but attempts will be made to suggest some useful general principles.

Of course, this question could be discussed on the basis of the list of indications for liver function tests given at the beginning of the chapter. To avoid overlapping, however, it is proposed instead to consider 4 fundamental factors governing the choice of tests:

1. The detection of liver damage in the absence of jaundice
2. The differential diagnosis of jaundice
3. Prognosis
4. The detection of excessive hemolysis

These reasons are not, of course, mutually exclusive and more than one may be relevant to any particular case. While some tests may be considered useful in all these categories, most are more appropriate to one or other class.

THE DETECTION OF LIVER DAMAGE IN THE ABSENCE OF JAUNDICE

This is in some ways the easiest group, since no test is specifically excluded, and at times any test may give useful information. The type of patient concerned is usually one with suspected cirrhosis or preicteric or posticteric hepatitis but alternatively may be suffering from some other disease, such as heart failure or thyrotoxicosis, in which liver involvement is anticipated.

The most sensitive and convenient tests to use are probably a selection from the excretory tests, such as serum bilirubin and the urine tests for bile pigments, together with one or two others such as the bromsulphthalein and the flocculation tests. In cirrhosis the serum albumin and globulin estimation probably will be required, and in different cases some other special test, such as galactose tolerance or hippuric acid, may be helpful. A small proportion of cirrhotics appear to give negative results to many tests, and these have been described as a special group of latent or asymptomatic cirrhosis by Sherlock[148] and by Ricketts et al.[134] In cases of this type the differential diagnosis often arises between cirrhosis on the one hand and hepatic carcinomatosis on the other. In this connection it is fortunate that the findings in the latter condition are usually distinctively different from those seen in the former. Secondary deposits in the liver usually cause a high serum alkaline phosphatase with considerable urobilinuria, and the protein tests tend to be normal. It should be noted, in parentheses, that similar results are found in liver abscess or amyloidosis. Later, obstructive jaundice may develop, of course; this is dealt with below.

In other diseases certain special tests have been found to be particularly appropriate for the investigation of hepatic involvement. Thus in thyrotoxicosis the oral galactose tolerance test and the hippuric acid test have given a high proportion of positive results, while most of the other tests are usually negative. In malaria, infectious mononucleosis and rheumatoid arthritis the flocculation tests are particularly affected, although some alteration in bromsulphthalein retention and coproporphyrin excretion has been noted also. In heart failure urobilinuria with positive flocculation tests is common, and jaundice may develop. A further discussion on liver involvement in other diseases is given at the end of the chapter.

Differential Diagnosis of Jaundice

Usually there is little difficulty in distinguishing hemolytic jaundice from the varieties. Thus the absence of bilirubin from the urine and the gross increase of fecal urobilinogen, together with a preponderance of indirect bilirubin in the blood and negative results with most other tests, make up a distinctive picture of excessive hemolysis. The diagnosis between obstructive and hepatogenous jaundice is, however, much more difficult. The selection of suitable tests to assist in this differentiation undoubtedly presents great difficulties, and the limitations of many tests in this respect have been exposed when too rigid an interpretation has been placed on the results. Quite a number of instances can be recalled of tests which orig nally were proposed as a solution of th problem, perhaps from the experience of small series of patients, only to encount failure when extended to a wider range cases. In spite of this it is the writer's opinio that liver function tests still have a usef contribution to make in this field.

The main difficulty is really the statistic one of dealing with the degree of overlap the results in the different types of jaundic Practically all the nonexcretory tests sho a higher average incidence of positive resul in hepatogenous as opposed to obstructiv jaundice, but if the overlap is too great th test becomes more or less valueless as a diag nostic aid. This would apply in general t hippuric acid, cholesterol, cholinesterase fibrinogen and amino acid estimations an to all the excretory tests, including brom sulphthalein.

Tests of limited value include serum pro teins, prothrombin estimations and galactos tolerance. Although some alteration of seru proteins may occur in obstructive jaundic particularly if complicated by malnutritio or infection, the changes are rarely very larg and gross alteration would favor hepatiti According to Wang,[162] minor changes hav no diagnostic value. The prothrombin is n always abnormal in jaundice, perhaps i about one third of the cases; but when it i the response to vitamin K is a valuabl pointer. Galactose tolerance is undoubtedl of value in cases with reasonably short his tories of jaundice—say up to 1 month—bu after this the chance of impairment, even i simple biliary obstruction, robs the test o diagnostic value unless the result is norma which would still favor obstruction.

During the last few years it has been ge erally agreed that the most valuable tests fo this special purpose are probably the seru alkaline phosphatase and the flocculatio tests. During the same period much work ha also been done on the choice of flocculatio test, and the advantages of combining thes two procedures has been pointed out by th writer and by others.[52, 98, 100, 111] At the sam time the limitations of this combination hav been recognized, and it may be said that thi recognition has played an important part i establishing the value of the tests, since s prevented the making of extravagant ims. It is most important to remember t probably no test or combination of tests ll give unequivocal diagnostic indications every case, but great use still can be made them if the equivocal and unequivocal mbinations can be clearly recognized.[100]

The general tendencies of the 2 tests have en referred to in detail above. The serum kaline phosphatase is almost invariably ove normal in biliary obstruction and fre- ently is over 35 King Armstrong units. It o rises in acute and chronic hepatitis but such conditions is usually below 35 units. the other hand, suitable flocculation tests e usually positive in hepatitis and are nega- e or at most only weakly positive in ob- uctive jaundice. In the writer's experience e best test for this particular purpose is the ymol flocculation test, which is particularly liable in giving negative results in biliary struction. As shown above, other tests, ch as the Takata-Ara or the cephalin cho- sterol, have a greater tendency toward posi- e results in obstructive jaundice and con- quently are less suitable for the present rpose.

The results of combining the serum alka- e phosphatase and the thymol flocculation sts in 200 cases of jaundice are shown aphically in Figure 41. It will be seen from is that all the patients with negative or 1+ ymol flocculation tests plus serum alkaline osphatase levels above 35 units had ob- uctive jaundice; in addition, all patients th normal phosphatases or strongly posi- e flocculation tests (2+ or higher) were nobstructive. This accounts for 80 per cent the cases, leaving 20 per cent in the shaded ea which includes all types of jaundice. esults of this type are unequivocal and do t assist in the differential diagnosis.

When this scheme was put forward it was garded as provisional, and the likelihood occasional exceptions to these rules was cognized (Maclagan[100]). However, very w exceptions have been seen by the writer, d although a small number have been corded in the literature by Coleman,[23] other iters have confirmed the value of the ymol-phosphatase procedure (Hoffbauer al.,[64] Wang[162] and others[62, 111]). There- re, it appears that we may accept the conclusion that this combination of tests will give useful indications of the type of jaundice in about 80 per cent of cases.

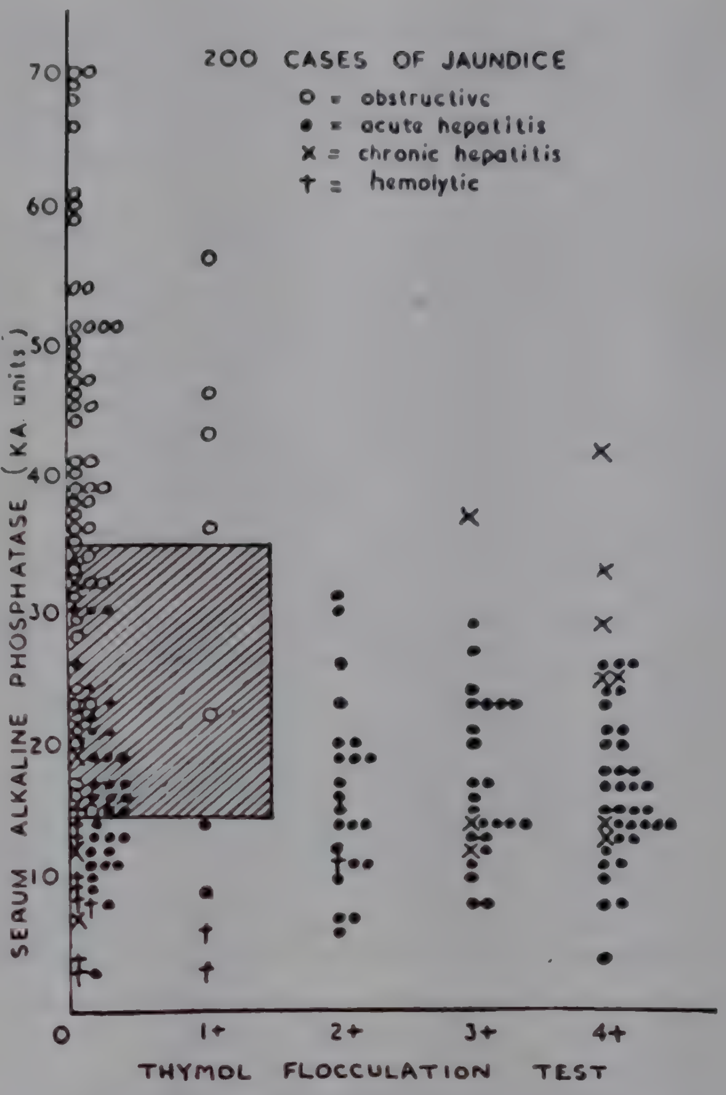


FIG. 41. Differential diagnosis of jaundice. (Maclagan, N. F.: Brit. M. J. 2:197)

The rationale of the procedure is far from clear, and it must be admitted that we have no accurate information as to why the effects of biliary obstruction, which can be quite damaging to many functions of the liver, are so small in the case of the flocculation tests and so striking in the case of the serum alkaline phosphatase. Perhaps we may hope that if ever this mystery comes to be solved it also may open the way to an even better functional differentiation between obstructive and nonobstructive jaundice.

PROGNOSIS

Exact information on the prognostic value of any test is difficult to obtain, as it involves correlation of the results with short-term or long-term follow-up studies, and few workers have been able to achieve this on a statistically significant scale. Therefore, the following account is based partly on fact and partly on impressions recorded in the literature which have not always been documented adequately.

A number of tests have definite prognostic association but do not add very much to the indications obtainable by clinical methods. Thus, the serum bilirubin level in hepatitis is correlated with the duration of jaundice (Sherlock[148]), but the intense jaundice of patients with high values will be obvious; moreover, such cases still may recover completely. Similarly high blood amino acids and low plasma fibrinogen values are seen only in very severe, usually irrecoverable liver damage, but such patients obviously are very ill, and a poor prognosis usually would be given on clinical grounds alone.

A reasonably good case has been made out for value of the serum albumin estimation in hepatitis. It is generally recognized that albumin synthesis is severely affected only with fairly gross liver damage, and low values indicate a poor prognosis. Thus Higgins et al.[61] showed in their series that most cases of hepatitis lasting more than 2 months had serum albumin levels below 3 Gm. per 100 ml., and regarded values of 2 Gm. and below as indicating severe and probably irrecoverable liver damage.

Failure of a low plasma prothrombin value to respond to vitamin K is also a valuable sign of severe liver damage. Usually, it has been recorded in jaundice due to subacute or chronic hepatitis, and such patients have a poor expectation of life.[69, 153]

We are perhaps on less certain grounds with the hippuric acid test. The work of Boyce,[12] mainly on surgical jaundice, directed attention to this test and suggested that excretions of less than 2 Gm. (oral method) indicated a poor operative risk and prognosis. This work was done before the prothrombin test became popular, and it is noticeable that since this time few further reports on the hippuric acid test in jaundice have appeared. Apart from jaundice, claims for the general prognostic value of the test in a mixed series of surgical and medical cases were made by Delor and Reinhart.[28]

They found that cases in both groups with low hippuric acid outputs had a high immediate mortality. No simultaneous renal fun tion tests were performed, and perhaps t results could have been correlated equal well with disturbed renal function. This wo also does not appear to have been repeat and remains unconfirmed.

It may be said in general that more wo needs to be done on this aspect of liver fun tion tests before the results can be interpret with precision. This would be well wor doing as the prognosis in cirrhosis is noto ously difficult at the present time.

DETECTION OF EXCESSIVE HEMOLYSIS

This section overlaps to some extent wi that on the differential diagnosis of jau dice, but, of course, excessive hemolys can often be demonstrated in the absence jaundice. This occurs in the hemolytic an mias, in pernicious anemia, in malaria, aft mismatched blood transfusion or certa hemolytic poisons, and during the absorptic of hematomata from any site such as fra tures of long bones. The findings are those hemolytic jaundice except that the seru bilirubin level is normal or only slight raised. Latent jaundice (serum bilirubin u to 3 mg. per 100 ml.) is fairly common these conditions, the pigment being main indirect, but the principal pigmentary abno mality is the gross excess of fecal urobilin gen. Some urobilinuria also may be presen the degree varying inversely with the state liver function. If the hemolysis is severe ar prolonged enough to cause anemia, reticul cytosis probably is present also. Pernicio anemia is an exception to this, but reaso for regarding the increased fecal pigment e cretion in this disease as a special case ar possibly not hemolytic in origin have bee given.

TESTS FOR ROUTINE USE

Having discussed the general principl involved, now it is necessary to make a fu ther choice of those tests suitable for routin application. Many different approaches hav been made to this problem, the most con plete being that of Watson,[63] who original advocated the use of 11 tests for jaundice and 7 for nonjaundiced patients, althoug this number was reduced later. He expresse the results in the form of his ingenious an

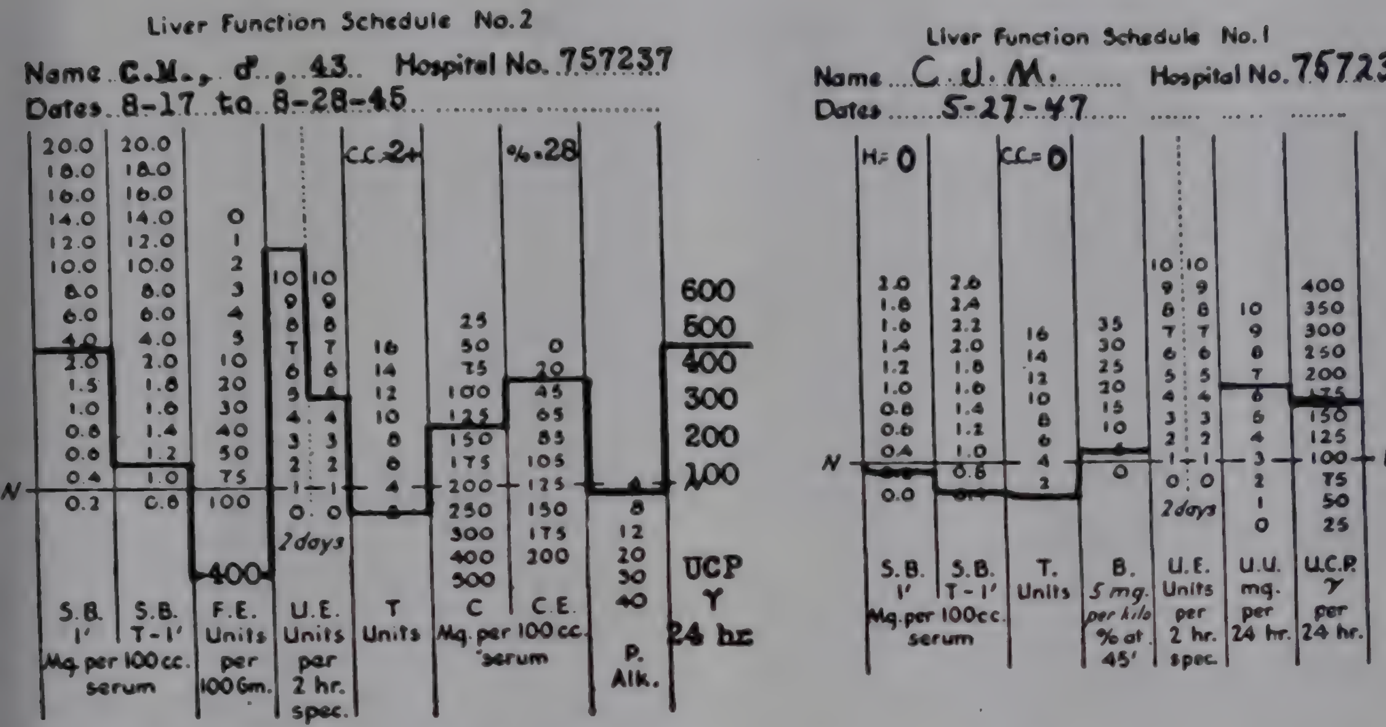


FIG. 42. Composite liver function studies in case 1. Key: S.B. = serum bilirubin, 1′ = prompt direct, T—1′ = delayed or indirect, F.E. = feces Ehrlich, U.E. = urine Ehrlich, T = thymol turbidity, C = total cholesterol, CE = cholesterol esters, P.alk = alkaline phosphatase in Bodansky units, UCP = urinary coproporphyrin, B = bromsulfalein, U.U. = urine urobilinogen, CC = cephalin cholesterol flocculation, H = Harrison text for bilirubin in urine (Barium strip modification), N----N = upper or lower limit of normal. (Watson, C. J.: Ann. Int. Med. 31:405)

ll-designed diagram (Fig. 42) which ows the normal for each test and gives the gree of abnormality as a profile. Thus the ture as a whole can be appreciated without erence to individual figures, and the differ- t types of functional disturbance can be ognized. However, the laboratory worker y well feel that the amount of labor in- lved in this scheme is at times somewhat cessive in relation to the significance of the ults, and he may look for a simpler ution.

The writer's present routine schedule is en in tabular form below and is designed be carried out in one afternoon visit of patient to the laboratory.

Routine Tests

1. Serum bilirubin, direct and indirect
2. Serum alkaline phosphatase
3. Flocculation tests (thymol, gold and c sulfate)
4. Urine for bile and approximate uro- inogen estimation on 2-hour specimen

Additional Tests, If Indicated

1. *In suspected cirrhosis* (nonjaundiced). Serum protein estimation. Bromsulphthalein test
2. *In obscure or preoperative jaundice.* Serum protein estimation. Prothrombin response to vitamin K
3. *In hepatic coma.* Blood amino acids

The 4 routine tests given here will record the intensity of any jaundice that may be present and in most cases will indicate the type of jaundice. In the absence of jaundice a number of the tests may be sufficiently positive to support a suggested diagnosis of hepatitis, cirrhosis, or hepatic metastases. In many cases, therefore, no further tests are required for diagnostic purposes.

If the results are negative or equivocal, or if prognostic information is required, one or two other tests are done according to the nature of the case as indicated. The serum protein estimation probably is required in any chronic case of hepatitis. In latent cirrhosis the bromsulphthalein is probably about the most sensitive single test, but in obscure jaundice it is replaced by the prothrombin estimations. In hepatic coma the amino acid level is important.

It will be noted that not all of the tests discussed in this chapter appear in the final list, and an element of individual preference obviously enters here. It may well be that others would prefer to add the cholesterol ester ration, the cholinesterase, or others. However, it is felt that the list given above includes most of the tests of established value, and that they are so arranged as to avoid too much unnecessary work. A minimum of 4 and a maximum of 6 tests which are within the capabilities of most routine laboratories represents an economy of labor as compared with more elaborate schemes.

TESTS FOR USE IN DISEASES NOT PRIMARILY HEPATIC

A considerable literature has now developed on the subject of functional disturbances of the liver in diseases not primarily hepatic, and it has been found in many cases that the tests most appropriate for routine use are not always those of most value in this connection. This is particularly true of thyrotoxicosis in which the functional cha are not at all obvious and can be der strated only by a few of the tests discu Some guide to those which have been successfully in this field is given in Tab

Results of this type are perhaps of r academic than practical interest, but have been of service in directing atter to the existence of liver pathology in t conditions. Thus in thyrotoxicosis damage is frequently present and prob is partly responsible for the onset of th toxic crisis, and in glandular fever jaun due to the associated hepatitis may occur heart failure the degree of failure is correl roughly with clinical severity and may contribute to symptomatology. Further cussion on this subject will be found u the relevant individual tests. The findings also of importance in their bearing on interpretation of results in cases suspecte primary liver disease, since allowance m be made for the possibility of secondary damage if any of the conditions liste Table 8 are present.

TABLE 8. LIVER FUNCTION TESTS IN DISEASES NOT PRIMARILY HEPATIC

DISEASE	TESTS USED	REFERENCE
Burns	Hippuric acid	Boyce[14]
Diabetes mellitus	Bromsulphthalein, flocculation tests	Gray et al.[50] Zimmerman et al.[187]
Heart failure	Urobilinogen, flocculation tests, serum bilirubin, bromsulphthalein	Bernstein et al.[10] Carter and M lagan.[17] Kissane et al.[80]
Infantile gastroenteritis	Prothrombin	Schlesinger, Payne and Burnard[140]
Infectious mononucleosis	Flocculation tests	Carter and Maclagan.[17] Cohn anc Lidman[20]
Malaria	Bromsulphthalein, cholesterol ester ratio, flocculation tests, urobilinogen	Carter and Maclagan.[17] Kopp and omon.[82] Lippincott et al.[89] Me hello and Drinberg[113]
Meningitis	Hippuric acid	
Obesity	Bromsulphthalein	Zelman[183]
Pulmonary tuberculosis	Bromsulphthalein	Hurst et al.[67]
Pneumonia	Hippuric acid, levulose tolerance, urobilinogen	Curphey and Solomon.[25] Menegh and Drinberg[113]
Rheumatoid arthritis	Bromsulphthalein, flocculation tests, hippuric acid, urinary coproporphyrin	Carter and Maclagan.[17] Darby.[27] R. et al.[133] Robinson[137]
Thyrotoxicosis	Galactose tolerance, hippuric acid	Althausen et al.[1] Haines et al.[54] Li mann.[87] Maclagan and Rundl Meranze et al.[114]
Spinal cord injury	Bromsulphthalein	Cooper et al.[24]

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hapter 6

NEEDLE BIOPSY OF THE LIVER

Leon Schiff, M.D., Ph.D., *and Edward A. Gall,* M.D.

Although puncture of the liver has been acticed for many years in the diagnosis d the treatment of hepatic abscess, the first tempt at diagnostic aspiration of liver tissue means of a syringe and a trocar is said to ve been made by Lucatello in 1895. Scat- red reports on the aspiration of liver tissue agments for diagnostic purposes between 07 and 1928 are recorded by Roholm, rarup, and Iversen. In 1939 Baron pub- hed his experience with 48 hepatic aspira- ons performed on 35 patients. He used a -cc. Luer-Lock or "Record" syringe and a -gauge needle about 9 cm. long. The inter- stal route was employed in several cases, t he preferred the subcostal approach, esuming this to offer less hazard of hemor- age. He appended a note to his report dicating that he had one death from hem- rhage directly attributable to the procedure a case of extensive metastatic carcinoma the liver. He found the method of value in e recognition of metastatic carcinoma of e liver and in the differential diagnosis of undice. In the same year (1939) Iversen d Roholm published their paper on aspira- on biopsy of the liver and their studies in ute epidemic hepatitis. These reports served an important impetus to the present-day e of the method.

METHOD

While various needles and procedural odifications have been proposed,[4, 8, 13, 14, 25, 32, 33, 36, 37, 45, 48, 49, 55] the technic most mmonly used in this country is essentially at of the transthoracic approach of Iversen d Roholm. The Vim-Silverman needle, a tting mechanism which originally was uti- zed by Tripoli and Fader[45] for hepatic biopsy via the subcostal route has proved to be the instrument of wide choice. The instrument recommended by the Danish workers produces a round, gaping puncture wound. Gillman and Gillman recommended that the point of the needle be beveled as with a hypodermic needle and not ridged as in the trocar tip described by Iversen and Roholm. The beveled point makes a short narrow puncture wound in the liver capsule. Its edges are in apposition, and it heals rapidly. Sheila Sherlock has had a large experience with the aspiration method but has employed a longer, narrower cannula with a bore of 1.0 mm. instead of the 2-mm. needle of Iversen and Roholm. The narrower cannula makes a smaller wound in the liver, and serious bleeding is less apt to occur than with the larger instrument. For a description of the technic that Dr. Sherlock employs, the reader is referred to her publication.[36] Dr. Sherlock makes it a practice to administer vitamin K to jaundiced patients for 3 days before the puncture, giving the vitamin parenterally in cases of obstructive jaundice and orally in cases of hepatogenous jaundice.

At the Cincinnati General Hospital needle biopsy of the liver is carried out on the wards, and the intercostal approach is used almost exclusively. The technic employing the Vim-Silverman needle (Fig. 43) as used by the staff of the Gastric Laboratory of the Cincinnati General Hospital is as follows:

> The upper limit of liver dullness at the end of expiration is suitably marked, and the point of biopsy selected one interspace below, between the anterior and the midaxillary lines. The point of entry is usually the eighth or the ninth intercostal space. The area chosen is sterilized with iodine tincture U.S.P., followed by 70 per cent alcohol and draped with sterile

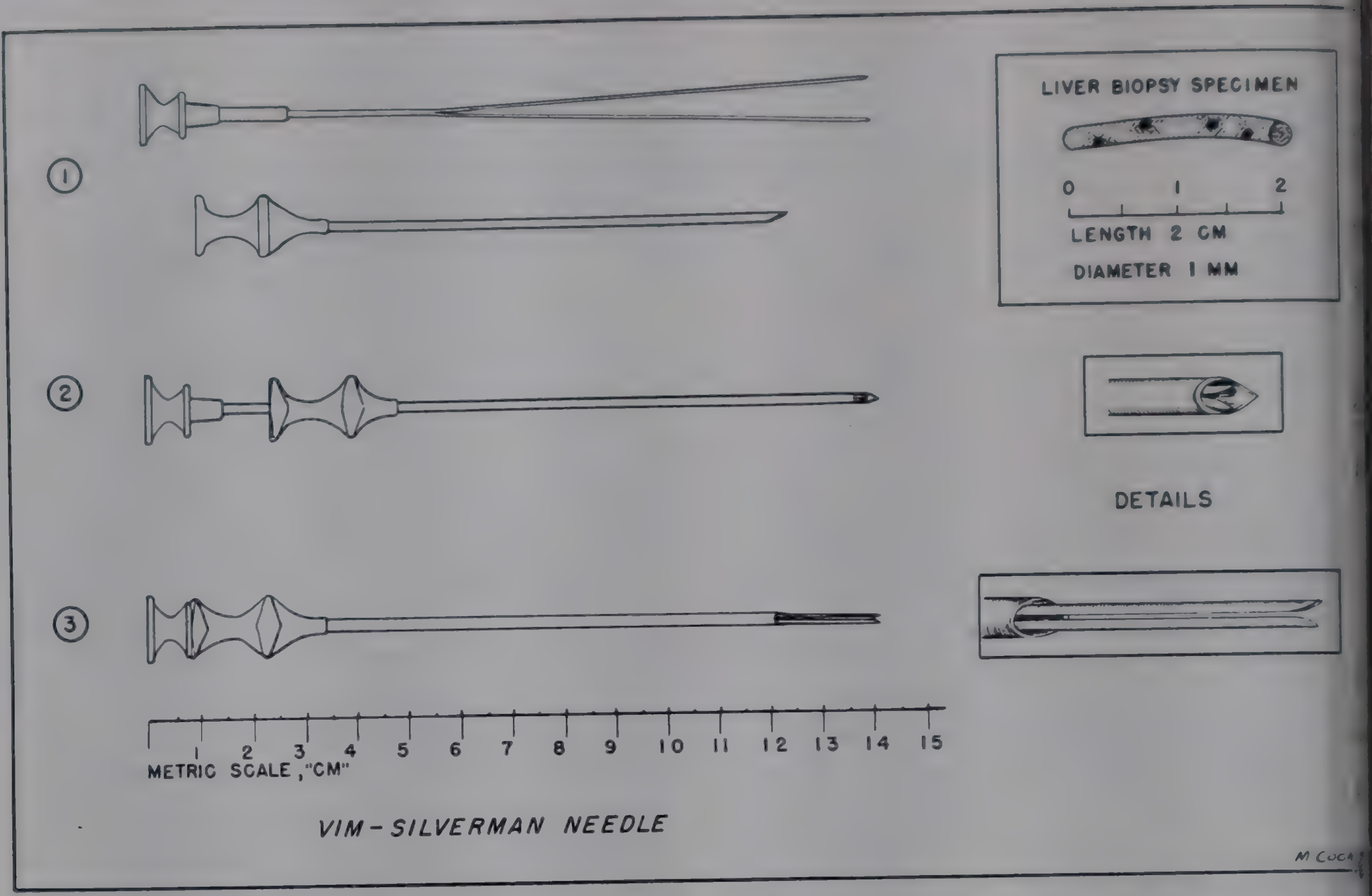

FIG. 43. The Vim-Silverman needle and average size of the biopsy specimen. (1) Shows the forked obturator removed from the outer cannula; (2) the position of the obturator as the needle is introduced into the liver; and (3) the position of the obturator as it cuts a tissue specimen. (McGregor Instrument Co., Needham, Mass.) (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

towels. The operator wears sterile rubber gloves. It is advisable to test the patient's ability to hold his breath after inhaling and exhaling deeply 3 times. The skin, the subcutaneous tissue, the intercostal muscle, the pleura, the diaphragm, Glisson's capsule and the hepatic substance are infiltrated with 2 per cent procaine hydrochloride solution, care being taken to penetrate beyond the intercostal space only while the patient is holding his breath at the end of full expiration. Approximately 8 cc. of procaine hydrochloride solution is used. A small incision is made in the skin over the procaine bleb with a No. 11 Bard-Parker blade to permit easy entry of the biopsy needle. *It is important that the needle be sharp.* The Vim-Silverman needle is introduced into the incision, with the forked obturator retracted back of the tip as first suggested by Hoffbauer. After the patient has inhaled and exhaled deeply 2 or 3 times, he is instructed to hold his breath at the end of complete expiration. The needle assembly is inserted promptly a distance of approximately 6 cm. (2 to 3 cm. into the substance of the liver) in a slightly downward direction. Then the obturator is pushed firmly until the final 1.5 cm. enters into the needle, while the latt is held steady. At this point *the obturator tip held steady while the carrier needle is advance over it with a rotating motion,* bringing th assembly back to its original relations but a vanced 1.5 cm. farther into the liver. This bor a cylinder of hepatic tissue which is usual 1 mm. in diameter and from 1 to 2 cm. length and grasps it tightly in the obturat fork. The entire assembly is rotated approx mately 90°, breaking the terminal attachme of the liver fragment, and then is withdraw (The average time elapsing between entry the Vim-Silverman needle into the substance the liver and its removal is from 5 to seconds.) A simple dressing is applied. Th patient is kept in bed on his back for 24 hou and observed carefully for evidences of hemo rhage. This is particularly important during th first 8 to 12 hours when hourly pulse and bloo pressure readings are desirable. Often a sy thetic vitamin K preparation, 10 mg. is admi istered parenterally a day before and for 2 3 days after the procedure is accomplishe (Recently Nelson has reported a detailed d scription of his method,[25] in which he uses

odified Vim-Silverman needle, to which the
ader is referred.)

Liver biopsy should not be attempted
less adequate facilities for blood trans-
sion are available. Some observers prefer
type and cross-match the blood of all
tients prior to the biopsy, but this has not
en our practice. Gillman and Gillman rec-
mmend that these biopsy procedures be
rried out under basal conditions in the
orning. They prefer a preparatory 12-hour
st in order to avoid the possibility of pene-
ation of a distended stomach. Obviously,
is is not a problem if the transthoracic route
employed.

For a long time we gave no preliminary
edication. At present we administer a hy-
odermic injection of 50 mg. of meperidine
Demerol) with 0.5 mg. of atropine about
minutes before the biopsy is performed.
cases with evidence of cholangitis it is
se to administer penicillin and streptomycin
fore and after biopsy.

About 1 in 5 patients will require medica-
n for pain following the procedure, but it
most unusual for an analgesic to be re-
ired after 24 hours. The patient is per-
itted to leave the hospital after 24 to 48
urs.

Failure to obtain adequate tissue for
oper interpretation may be a problem in
practiced hands. However, with experi-
ce, failures of this type should be mini-
ized. We have had no hesitation in making
immediate second effort to procure a
itable specimen if the original yield has
peared to be grossly unsuitable.

Recently, Terry[44] has emphasized the
agnostic value of gross inspection of the
opsy specimen. Sherlock previously pointed
t that specimens obtained from fatty livers
ve a greasy look; those removed from cir-
otic livers tend to crumble into fragments
th a lobulated contour; and those obtained
om malignant deposits have a dull, white
pearance. Terry has devised a modifica-
n of the apparatus used by Gillman and
llman with needles having an internal
re of 1.65, 1.8 and 2.1 mm. This method
said to have the advantage of providing
ge intact specimens which are handled
sily and examined readily with the naked
e or with a hand lens. The tissue may be placed upon nonglossy paper or upon a cover slip, a medium that facilitates transillumination. Terry has recommended also the introduction of the tissue core into a glass tube 5.0 cm. long with a 4.0 mm. bore. Thus it can be handled freely without damage, and the glass offers the added advantage of slight magnification and facility of transillumination. Obviously, the caliber of the trocar, larger than that of the Vim-Silverman needle, offers a greater hazard of hemorrhage, although Terry reports that in over 300 cases he has had neither hemorrhage nor other fatal accident. In a single instance, a patient with intrahepatic biliary obstruction, there was bile peritonitis from which recovery ensued.

The specimen must be examined without delay and before fixation in order to avoid opacification. The fragment of normal liver, according to Terry, has "a mild chocolate hue, which varies in depth with the concentration of glycogen and which on closer inspection is seen to be slightly mottled, the darker areas corresponding to the central zones. The specimen is opaque to transillumination and no vascularity is visible within the tissue. In obstructive jaundice the specimen has a speckled appearance . . . against a background paler than normal, the central zones appear as dark green irregular spots up to 1 mm. in diameter. . . . This green speckling . . . is occasionally observed in hepatitis with marked biliary stasis, especially the cholangiolitic type. . . . In viral and toxic hepatitis and in jaundice complicating cirrhosis, the specimen is pale and uniformly icteric, without any green speckling. . . . In hemochromatosis the biopsy specimen is unusually brown in color. . . ."

In Boeck's sarcoid and in miliary tuberculosis the tubercles are not apparent on superficial examination, but if the specimen is transilluminated the rounded granulomas usually are detected, for they are brightly translucent and contrast sharply with the opaque normal tissue. It is Terry's contention that the gross demonstration of these translucent foci may be as helpful as the microscopic examination for correlation with clinical findings. He points out that detection of the lesions also indicates at once that the biopsy has been successful.

Despite the advantages claimed for this method it is doubtful that naked eye appraisal of these specimens can supplant critical microscopic evaluation. Moreover, it appears unlikely that the "combined instrument" provides either greater safety or more suitable tissue yield than the Vim-Silverman or the narrower 1-mm. Iversen-Roholm needle.

CONTRAINDICATIONS

The following should be considered contraindications to needle biopsy of the liver:

1. An Un-co-operative Patient. This was first emphasized by Sherlock. There must be a certain ability and willingness to follow instructions. This is particularly pertinent to breathing at the time the specimen is actually cut during transthoracic biopsy. Stuporous, delirious, psychotic and comatose patients naturally should be excluded.

2. Depleted Prothrombin Content. A blood prothrombin level of less than 50 per cent of normal value or the presence of a blood dyscrasia with hemorrhagic tendency constitute serious hazards.

3. Local Infection. Infectious conditions in the lower lobe of the right lung or the pleural cavity may be carried into the liver or the peritoneum. The presence of peritonitis also represents a contraindication for similar reasons.

4. Ascites. This increases the difficulty of obtaining a satisfactory tissue specimen, particularly in cases of hepatic cirrhosis. Paracentesis with reduction of abdominal fluid should be done before the biopsy is attempted.

5. High-Grade Extrahepatic Obstructive Jaundice. This is especially hazardous in the elderly patient with an enlarged palpable gallbladder. The intrahepatic biliary pressure is apt to be high under such circumstances (Hoffbauer[15]). Bile leakage from the puncture wound in the liver or from a penetrated bile duct may result in bile peritonitis.

6. Marked Anemia.

7. Prolonged Bleeding from the Skin Incision at the Time of Biopsy. Terry advises postponing the biopsy if cutaneous bleeding lasts more than 10 minutes. He believes that this precaution has avoided carrying out biopsy in patients with abnormal bleedin tendencies in association with uremia, thrombocytopenia and low prothrombin leve which were reported incorrectly as normal c fell suddenly from normal. Zamcheck an Klausenstock also have abandoned the performance of biopsy when bleeding from th preliminary nick of the skin is prolonged unduly. We, too, have adopted this practice.

REACTIONS AND COMPLICATIONS

1. Pain at the site of entry with extensio to the right shoulder at the time of the biops procedure may follow. In our experience thi occurs in about a fourth of the patients an usually is mild and transient. Pain has bee reported variously in 5 to 50 per cent of patients.[14] The right shoulder pain probably i due to the presence of a small amount o blood on the undersurface of the diaphragm.[10] Pain in the right hypochondrium may indicate a subcapsular accumulation o blood or bile.[17] In one of our patients ther was pain over the entire right chest shortl after the specimen was removed. Exaggerate by respiration, the pain was present for mor than an hour after the biopsy was completed no abnormalities were detected on physica or x-ray examination of the chest.

2. Epigastric discomfort or pain may b experienced during the time the needle is i the liver substance or for a period afterwar and sometimes is described as a feeling o having one's "wind knocked out." A frictio rub occasionally develops in the region of th biopsy site. While usually of short duration the rub may last for several weeks.

3. Hemorrhage into the Peritoneum. Although uncommon, this is the chief fatal complication of liver biopsy. Most cases of fata hemorrhage have resulted from perforatio of distended portal or hepatic veins or aberrant arteries.[56] In some cases a tear in th liver occurred when the patient breathe deeply while the needle lay in the liver. Hemorrhage usually is manifest within 24 hour after performance of the biopsy. Fortunately it ordinarily ceases spontaneously and shoul be controlled by blood transfusions.

Through the peritoneoscope postbiopsy bleeding has been observed to consist of a thin trickle from the puncture wound in the

ver. It lasts only 10 to 20 seconds and totals
to 10 cc.[16] In 2 patients who died of unre-
ted causes 13 and 24 hours after biopsy,
oholm, Krarup, and Iversen noted small
unctate wounds in the liver and a table-
oonful of blood in the peritoneal cavity in
ach instance. After longer intervals in other
ases there was no stigma of the needle punc-
ire, and no blood was visible in the abdom-
nal cavity. In a patient with hepatic metas-
ises from a carcinoma of the gallbladder
ese observers found a "palm-sized" coag-
lum over the upper surface of the liver at
ecropsy done 24 hours after the biopsy.

Terry[43] found serious significant hemor-
hage recorded in 16 (0.2%) of 7,532 re-
orted biopsy cases which he reviewed. Lap-
rotomy was required in 4 patients, trans-
sion alone in 3, and expectant treatment
fficed in 9. We have encountered serious
emorrhage 4 times in over 1,300 patients
ho have had liver biopsy. Repeated blood
ansfusions were required in all 4 patients,
nd laparotomy was necessary in one. All re-
overed.

4. Bile Peritonitis. This complication ap-
arently occurs only in the presence of ob-
ructive jaundice and probably reflects the
ccompanying biliary tract infection. Terry
ported 11 cases in his survey of the litera-
re.[43] Laparotomy was required in 3 of 7
ases in one series. One fatality was reported
mong 4 other recorded instances. Hoff-
auer[15] has stressed the importance of early
cognition in order to initiate prompt sur-
cal decompression of the bile duct system
necessary. The complication developed re-
ently in one of our patients—a woman of 79
ears of age with common duct stone. At this
riting this represents our sole fatality di-
ctly attributable to liver biopsy.

**5. Hemorrhage into the pleural cavity or
eural effusion** has been reported to result
om injury to the pleura or penetration of an
tercostal vessel. Arterial injury can be
oided by keeping the needle close to the
wer border of the intercostal space. Passage
ascitic fluid into the thorax through a
edle perforation of the right leaf of the
aphragm with mild respiratory embarass-
ent has been reported in 3 instances.[56]

6. Pneumothorax has occurred twice in
r experience, and in both instances the symptoms were mild, and the pulmonary collapse did not exceed 10 per cent.

7. Severe apprehension associated with various nervous and hysterical manifestations may be observed on rare occasions. When these become evident as the procedure is begun, biopsy should be postponed.

8. Shock may occur uncommonly after the procedure. Kleckner and associates reported 2 cases of transient pleural shock lasting from 1 to 2 hours after biopsy. Fatal shock, not explainable on the basis of blood loss, has been described in two instances.[56] Roholm, Krarup, and Iversen encountered mild shocklike states 3 times in performing 297 biopsies. These authors considered these similar to those exhibited by nervous and apprehensive patients following venipuncture. Kleckner[20] recently reported "pleural shock" in 8 cases among a total of 145 consecutive liver biopsy procedures, some of which were carried out transabdominally. We know of 2 other instances of shock, one of which occurred in our own series. In both cases the subjects were elderly males with obstructive jaundice. Our patient had common duct stone with suppurative cholangitis and multiple liver abscesses, while the other patient had a carcinoma of the ampulla of Vater.

9. Procaine reactions have been reported by Nelson but have not been encountered in our own experience.

10. Fatal pulmonary bile embolism has been reported following aspiration needle biopsy in a patient with carcinoma of the ampulla of Vater.[6] This need not necessarily be considered a complication of needling, since we have observed 2 instances in which it occurred spontaneously in patients with high-grade biliary obstruction and infection.

11. Tumor Seeding. Implantation of tumor cells in the needle tract has been reported.[39, 40] We have not observed this phenomenon.

12. Penetration of Abdominal Viscera. Theoretically, this is apt to occur less frequently following transthoracic biopsy than with utilization of the anterior route. Hoffbauer[14] noted a case of perforation of the colon with fatal peritonitis following needling by the subcostal approach. Baron recovered a piece of colonic mucosa without

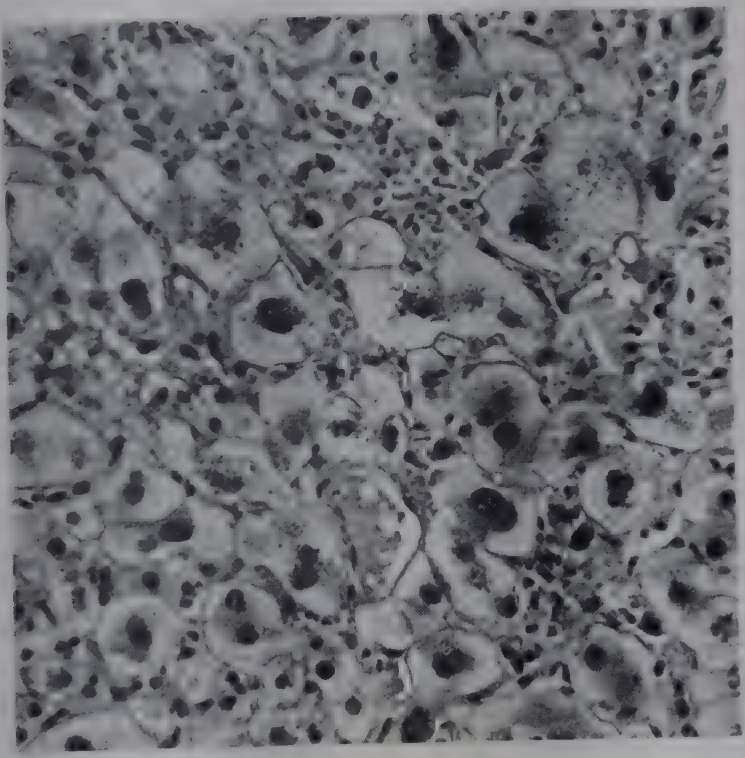

FIG. 44. Acute viral hepatitis. A high-power view, demonstrating swollen parenchymal elements ("balloon cells") with ground-glass cytoplasm and amitotic nuclear division. Focal inflammatory aggregates are evident, but the liver cells exhibit no fatty vacuolization.

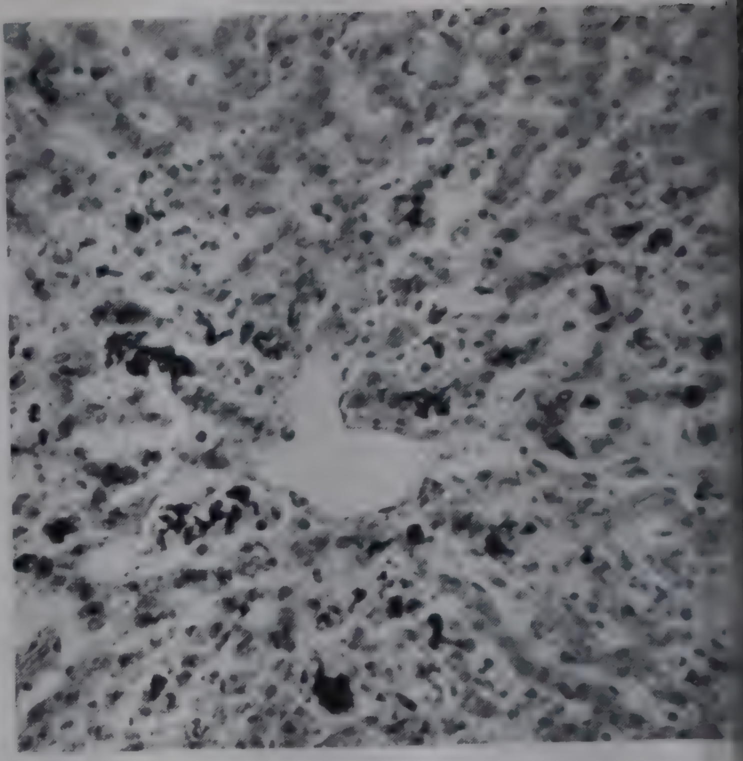

FIG. 45. Obstructive bile stasis, carcinoma of the head of the pancreas. In the centralobular region intercellular bile capillaries are brought into prominence by the dark-staining inspissated plugs of static bile. Liver cells are small and exhibit none of the features observed in viral hepatitis.

serious consequence. Reynolds had a similar experience; in his case there was no evidence of peritonitis at laparotomy 3 days after biopsy. Perforation of the gallbladder is also rare. Gamble and Sullivan report 2 cases of accidental gallbladder biopsy using the intercostal approach. There were no serious consequences.

CLINICAL APPLICATION

The needle method has proved to have considerable application in the clinical evaluation of hepatic disease.[35] Indeed, many misconceptions of long standing have been clarified, and the understanding of liver ailments has attained a high level in a relatively short period. The following represent some of the many avenues which have been entered.

1. The Exclusion of Hepatic Disease in Apparent Hepatomegaly. An incorrect presumption of hepatic disease is common when the liver is palpable, particularly in a patient with a prolonged history of alcoholism or one who is known to have a malignant tumo which may have metastasized to this orga Normally, the liver may extend from 1 to fingerbreadths below the costal margin an may be displaced downward in individual with pulmonary emphysema or right pleura effusion. When possible, the determinatio of the upper border of liver dullness is helpfu in assessing the size of the organ.

2. The Exclusion of Hepatic Disease i the Presence of Abnormal Liver-Functio Tests. Abnormalities of one or more live function tests are encountered not infrequently in the absence of liver disease. Thi may result from alterations in blood protein which affect the cephalin-cholesterol flocculation and the thymol and zinc turbidity tests Abnormal bromsulphalein retention is encountered in the presence of fever, shocklik states, or in older persons without demonstrable liver disorders.

3. The Distinction Between Medical an Surgical Jaundice. The histologic change characterizing viral hepatitis[1, 9, 23, 30, 38,] and those related to obstructive jaun

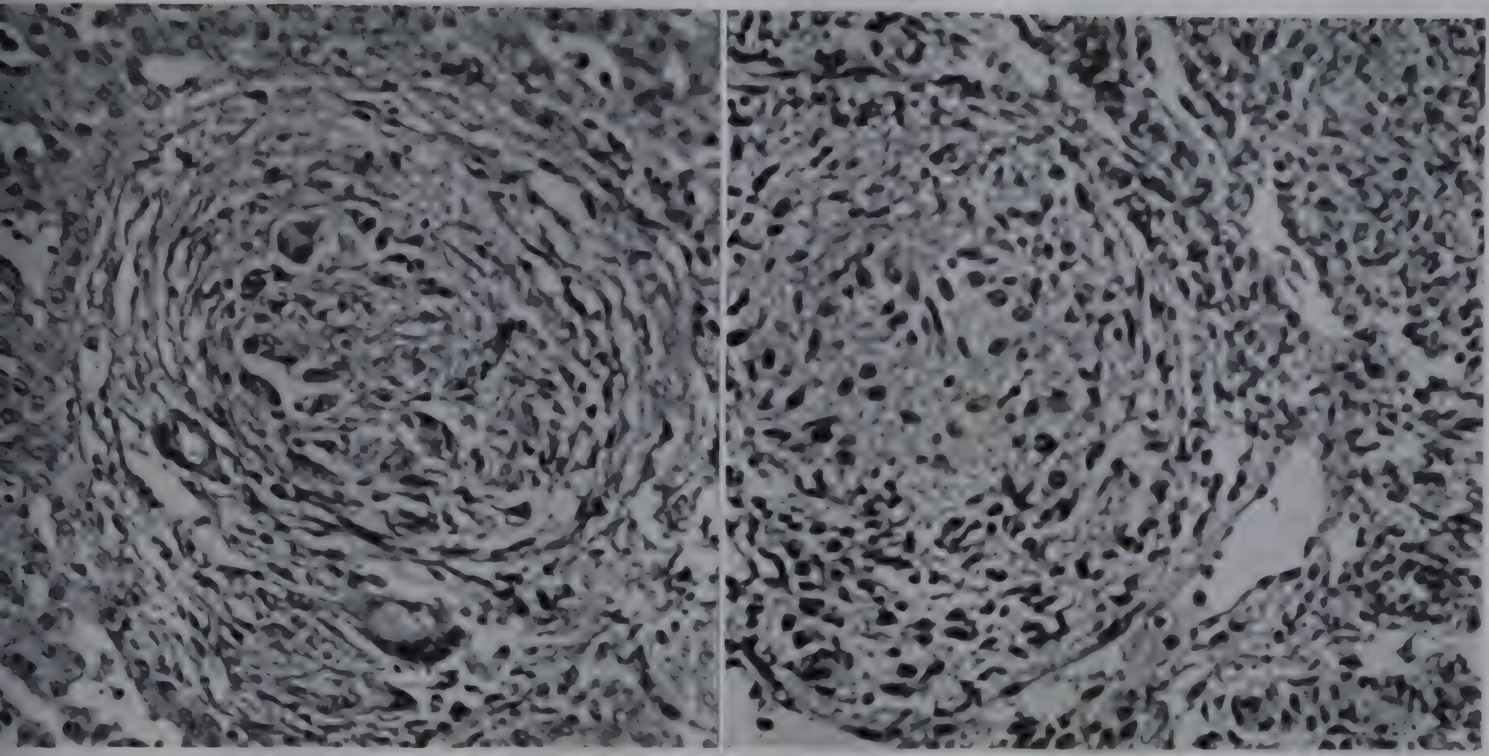

FIG. 46. (A, *Left*) Miliary tubercle. Sarcoidosis. The lesion is characterized by concentrically arranged epithelioid cells interspersed among which may be seen inflammatory giant cells. There is little peritubercular inflammatory cell reaction. (B, *Right*) Miliary tubercle. Tuberculosis. An early caseation appears in the center of the tubercle. Surrounding it is a pronounced lymphocytic exudate. The lesion is nondiagnostic but consistent with tuberculosis.

ce[24, 26, 29, 53] have been well described by any authors. Morphologic differentiation etween the two conditions is almost always ossible (Figs. 44 and 45). The distinguishg features are most pronounced during the st few weeks of icterus but are usually recgnizable in the later phases, although certain the histologic criteria may be obscured.

4. Observations of the Natural Course of iver Disease. The disappearance or persistice of manifestations of viral hepatitis or e development of cirrhosis are ascertained est by means of liver biopsy. The clarificaon of the so-called posthepatitis syndrome id its differentiation from chronic or relapsg hepatitis is approached best by this eans. The evaluation of the fatty liver and e determination of its relation to cirrhosis n be investigated only by biopsy.

5. The Evaluation of Effectiveness of herapy. Several authors have remarked the lue of the liver biopsy in determining the fects of various forms of therapy.[42, 49, 50] otable among the conditions that may be vestigated in this manner are the fatty liver, emochromatosis and even tuberculosis.

6. Elucidation of the Cause of Hepatomegaly. The liver may be enlarged as the result of many different lesions—a number of which may remain obscure without recourse to histologic study. Among these may be listed the fatty liver, anicteric hepatitis, cirrhosis, granulomatous disease, hemochromatosis, aleukemic leukemia, extramedullary hematopoiesis and fungus disease, to mention some of those which have come to light among our own cases. In our experience the needle specimen has pinpointed repeatedly the nature of an ailment or, equally important, has served to exclude one which was incorrectly believed to be present.

7. Distinction Between Intrahepatic and Extrahepatic Portal Vein Obstruction. This has attained a level of considerable importance since the advent of vascular shunt procedures in the relief of portal hypertension and collateral venous abnormalities. The practical value of determining the desirability and the potential risk of operation in relation to the presence or the absence and the nature of underlying hepatic disease should be obvious. In like fashion the preferential site of operative incision (portocaval vs. splenorenal shunt) may be predicated upon the

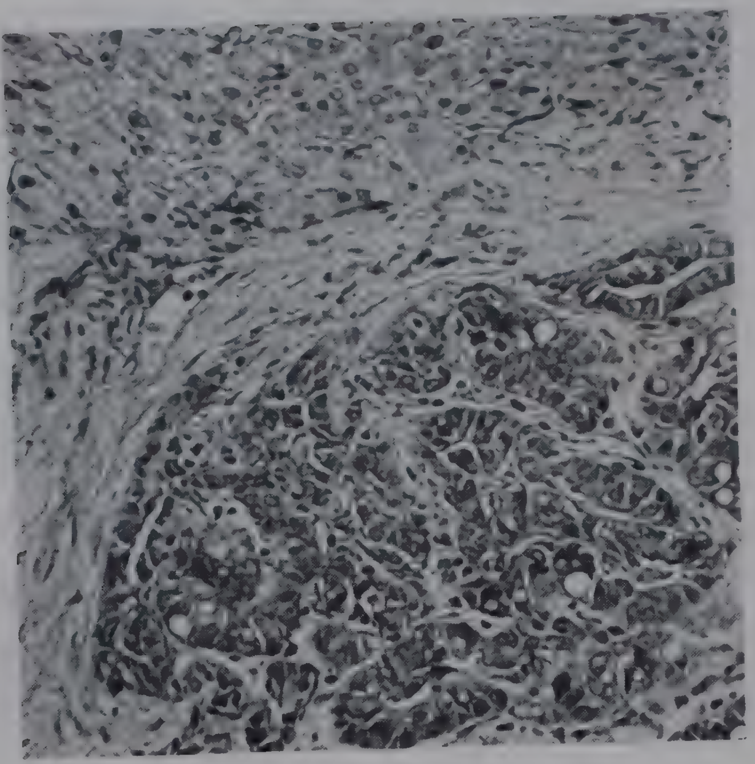

FIG. 47. Metastatic carcinoma. Neoplastic epithelial cells exhibit abortive efforts at acinus formation. The primary site proved to be in the gallbladder.

nature of the changes in the liver. Naturally, the biopsy cannot indicate the character or the location of the vascular occlusion in those instances in which the liver is not the site of venous impingement.

8. The Recognition of Granulomatous and Other Systemic Inflammatory Disorders. The liver often participates in a wide variety of infectious diseases of systemic character. Liver biopsy may bring one or another of these to light when there is no clinical suspicion of its existence (Fig. 46A). Notable among these ailments are the tubercular granulomatous processes of which tuberculosis, brucellosis, sarcoidosis, syphilis and fungus disease are important and common examples.[2, 7, 11, 19, 34, 41, 46, 47] Usually the character of the lesion is such that a definitive etiologic basis cannot be established from the specimen alone, although in a few instances the causative agent may be demonstrated by stain or culture. On the other hand, the detection of a tubercular process may serve to initiate pertinent clinical tests that will lead to clarification (Fig. 46B).

9. Detection of Intrahepatic Neoplasm. The needle biopsy method has been surprisingly fruitful in the demonstration of primary or metastatic neoplasm in the liver (Fig. 47). It is of particular value in verifying the pre ence of suspected tumor but also has fr quently brought to light neoplasm when non was considered to be present. In a recer study of 111 cases in which intrahepatic nec plasm was ultimately proved, the biopsy pro duced a positive yield in 82 instances.[51] I those cases in which an initial specimen ha been unrevealing but in which neoplasm wa strongly suspected a second or even a thir attempt has been justifiable in order to estab lish the correct diagnosis.

Positive results have been obtained wit equal frequency with either the lateral inter costal or the anterior abdominal approach Our results would indicate that frequently smooth liver may yield a positive specimen On the other hand, occasionally we have ha great difficulty in procuring a positive biops from a nodular liver which later proved t be riddled with metastatic carcinoma!

10. Clinical Research. The potential valu of transcutaneous biopsy in the investigatio of both the normal and the diseased live appears to be unlimited.[55] The metabol activities under physiologic conditions, th progress of disease and the effect of thera peutic agents are all susceptible to study b this means. The method has been employe in the study of hepatic enzyme activity[52] an in the biochemical investigation of lipid util zation.[5, 55] A micromethod has been de scribed for the determination of vitamin content in the liver in human subjects. Evaluation of the effect of antibiotic therap upon active tuberculosis also has bee carried out.[28]

Obviously, the needle biopsy method not without its limitations. The procedure relatively safe, but deaths have followed i use. In a survey of the literature comprisin over 10,000 needle biopsies, Terry listed mortality of 0.12 per cent and an inciden of major complications of 0.32 per cent. In a review of 20,016 needle biopsies of th liver Zamcheck and Klausenstock reporte a true mortality of less than 1:1,000. Wi selective observance of the contraindication enumerated serious complications shou constitute a negligible risk. We have foun that the experienced individual is much le prone to encounter difficulty or to submit a unsuitable specimen. Therefore, in our ow

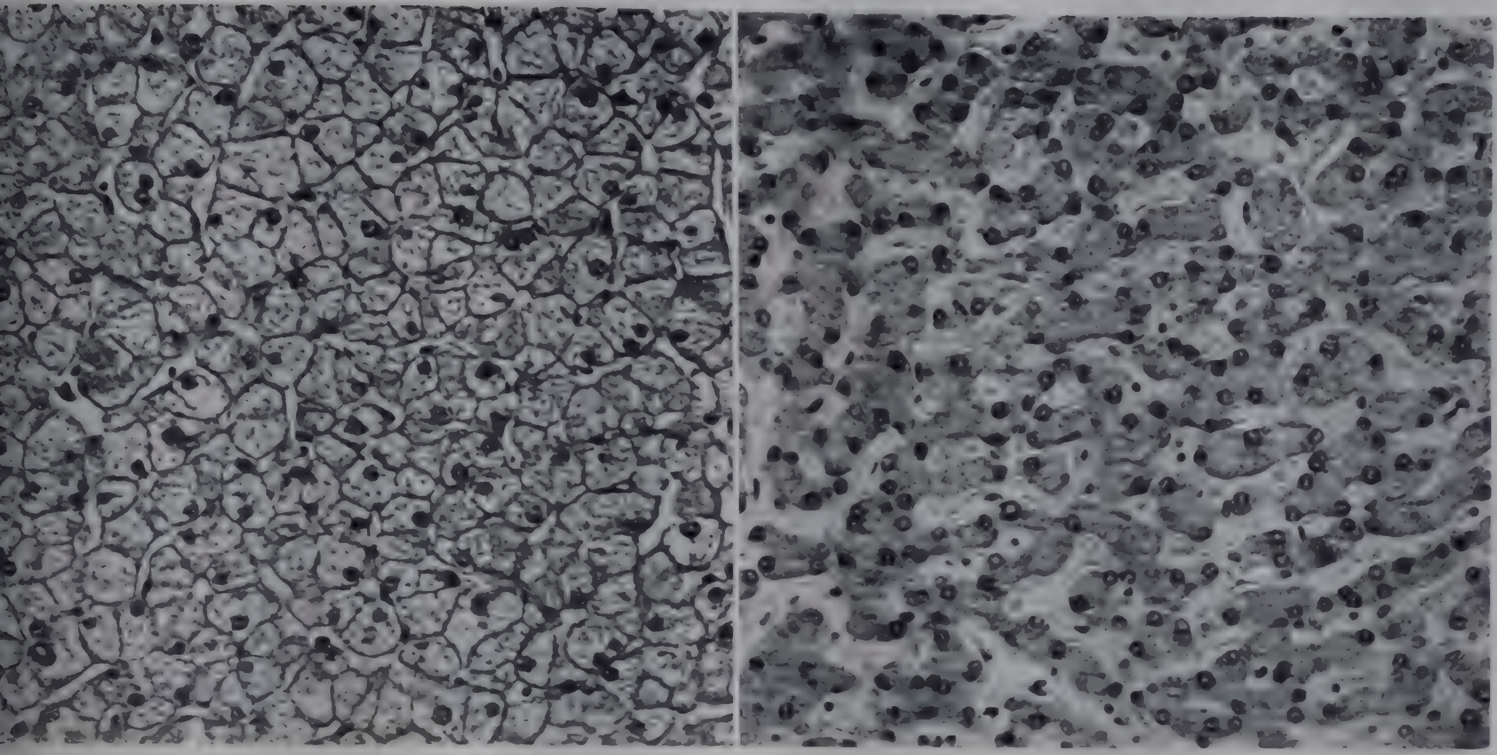

FIG. 48. (A, *Left*) Normal liver—needle biopsy specimen. A high-power photomicrograph, revealing narrow sinusoids, sharply demarcated parenchymal cells and characteristic ground-glass clarity of cytoplasm. Hematoxylin and eosin stains. (B, *Right*) Normal liver—autopsy specimen. The contrast with the biopsy specimen is readily apparent (magnification is identical). Sinusoids are wide, and a space is perceived between endothelium and liver cells. The latter appear shrunken and contain a smudgy opaque cytoplasm. Cell margins are inapparent. Specimen procured 5 hours postmortem; death due to malignant hypertension and acute pyelonephritis. Hematoxylin and eosin stains.

stitution we have avoided permitting any ut adequately trained and responsible perons to carry out the needle biopsy.

The smallness of the specimen has been aimed by some to limit its value. However, e and others have found the narrow core tissue to be quite representative in diffuse ver disorders. Indeed, we have come to efer the Vim-Silverman instrument in the rocurement of specimens during surgical ploration. The ordinary wedge section reoved by the surgeon has the disadvantage reflecting, on the one hand, the nonspecific stortions common to the subcapsular gions and, on the other, acute inflammatory actions to the immediate surgical maniputions. A better appraisal of the status of the ver can be obtained from a specimen reoved from its depths.

A minor problem in the histologic interetation of biopsy specimens derives from e rather impressive difference in appearce of tissues promptly fixed in the living ate from those procured at necropsy in hich postmortem alterations usually are advanced. This need not be a serious matter but it justifies remark in view of the occasional instance in which individuals accustomed to autopsy material have interpreted the normal biopsy specimen as an abnormal one. In the biopsy section parenchymal cells are outlined sharply and lack the smudgy opacity evident in most postmortem tissues. Indeed, the normal clarity of staining has been misinterpreted as indicative of vacuolization. However, it is believed to indicate a preservation of glycogen and an absence of "cloudy swelling" commonly occurring during the agonal state. Sinusoids are not as readily apparent, and the cordlike quality of the liver plates is obscured (Fig. 48A, B). A familiarity with these and other characteristics of biopsy tissue is readily attained.

While liver biopsy obtained at peritoneoscopy offers the advantage of visualization of the liver surface and thus choice of a biopsy site, specimens so obtained rarely gather tissue more than 3 to 4 mm. deep to the capsule unless a specially designed Vim-Silverman needle is employed. Peritoneoscopic examination is a much more formidable procedure. It must be performed in an operating room; it requires the creation of a tense pneumoperitoneum; and usually it is followed by much more discomfort than transmural needle biopsy.[15] Furthermore, it entails a greater risk to the patient.

For a long time disorders of the liver have been beclouded by inexact clinical pronouncements, by retrospective speculations derived from study of advanced lesions in a postmortem state, and by overly zealous faith in the results of so-called liver-function tests. The contribution that has been made to the modern dynamic concept of liver disease by the transcutaneous biopsy method has been incalculable. One may not gainsay the value of intelligent clinical appraisal and th proper interpretation of accurately pe formed laboratory tests. Nonetheless, th liver biopsy constitutes a keystone in th arch of the understanding of liver diseas Volwiler, Jones and Mallory have apt remarked:

> The most careful clinical scrutiny of a p tient with any chronic hepatitis may not perm one to predict with even moderate accuracy th histologic phase of the liver disease preser Neither do any laboratory tests, even when r peated serially, always correctly reflect the tr histologic state of the liver at a given time, the changes taking place during clinical ob servation; frequently the only means of dete mining this is microscopic examination of a tual liver tissue.

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hapter 7

JAUNDICE

Leon Schiff, M.D., *Ph.D.*

GENERAL CONSIDERATIONS

Jaundice, or icterus, is the condition rec-
gnized clinically by a yellowish discolora-
on of the plasma, the skin and the mucous
embranes caused by staining by bile pig-
ent. Frequently it is detected best in the
eripheral portions of the ocular conjunc-
vae and also can be observed in the mucous
embrane of the hard palate or in the lips
hen compressed with a glass slide. It may
overlooked in poor or artificial light. It
ay be preceded for a day or more by the
ssage of dark urine or light-colored stools.
terus may be detected by the skilled ob-
rver when the concentration of serum
lirubin reaches 2 mg. per 100 cc. and is
vious to the most unobservant when the
ncentration exceeds 7 or 8 mg. per cent
Gray).

Usually, it has been accepted that biliru-
n is derived exclusively from the hemo-
obin of mature red blood cells and that it
formed in the reticuloendothelial cells of
e bone marrow, the spleen and the liver.
normal man about 250 to 300 mg. of
lirubin should be produced daily from the
moglobin of destroyed red cells.[66] Recent
udies based on the use of N^{15}-labeled
ycine indicate that in normal man at least
to 15 per cent of total bile pigment is
rived from one or more sources other
an the hemoglobin of mature circulating
ythrocytes.[67] Investigation of the nature of
ese alternative sources has revealed that
matin and perhaps protoporphyrin can be
nverted to bile pigment in the mammalian
ganism.[66] For discussions of hemoglobin
tabolism and the chemical mechanism of
le pigment formation the reader is referred
the works of Lemberg and Legge,[64]
ith,[122] and Gray.[39]

The precise form in which bilirubin is transported in the blood from the cells of the reticuloendothelial system to the liver in the normal or jaundiced person and that in which it is transported to the kidney for excretion remain undetermined.[39] The mechanism by which indirect-reacting bilirubin is converted to the direct form in both obstructive and parenchymal jaundice after passage through the liver is still unknown. Controversy exists as to whether there are one or two forms of bilirubin, as based upon the van den Bergh reaction. The recent studies of Klatskin and Drill,[57] Gray and Whidborne,[41] With,[121] and Deenstra[23] fail to support the view that there are two forms of bilirubin. On the other hand, Najjar and Childs have succeeded in crystallizing an indirect-reacting bilirubin; they report that this form is precipitated with the globulin fraction on ammonium sulfate fractionation, while the direct-reacting bilirubin is precipitated with the albumin fraction. They suggest that the direct bilirubin may be a metal complex. Cole, Lathe and Billing believe that the indirect-reacting pigment is bilirubin, while the direct-reacting fraction is a mixture of 2 pigments other than bilirubin. They have been able to separate these 3 pigments on reverse-phase chromatograms. Watson[112] would reconcile the differences obtained by various workers on the basis of differences in the chemical manipulations of bilirubin-containing sera. He would consider the possibility that a differing physical state of the bilirubin in direct-reacting sera rather than a structural difference might influence its behavior in the chromatographic method used by Cole and his co-workers.

In spite of the controversy over the mechanism of the van den Bergh reaction, it is clinically useful to determine the 1-minute as well as the total or 15-minute serum bilirubin by Ducci and Watson's modification of the method of Malloy and Evelyn. This is well borne out by the report of Zieve and associates, who have shown that the 1-minute bilirubin is more effective than the total bilirubin in detecting an individual with liver or biliary tract disease, especially in those diseases in which severe jaundice is relatively infrequent, such as cirrhosis, congestive failure and a group of miscellaneous disorders.

In the older literature it was often stated that the renal threshold for bilirubin was 2 mg. per 100 cc. The threshold has been found to be quite variable in hepatitis, not only from case to case but at different stages of the disease.[125, 126] It is lower during the preicteric phase and higher during the recovery phase.[39, 90, 125, 126] Bilirubinuria is often noted in the preicteric phase of hepatit when the total bilirubin is within norm limits.[125, 126] Zieve and his associates hav shown that bilirubinuria is not dependent the total serum bilirubin concentration, ar although not correlated with any given lev of the 1-minute bilirubin, it has been ol served only when the prompt-reacting bilir bin is increased. Failure of excretion bilirubin in the urine in cases of regurgit tion jaundice may result from impaired ren function.[39, 88, 125, 126] In cases of hemolyt jaundice bilirubin may fail to appear in th urine, even though the total serum concer tration may exceed 16 mg. per cent.[24, 40, 1]

The principal function of the liver wi reference to bilirubin is that of excretion. this process bilirubin of the indirect type converted to the direct type. After it ente the small intestine the bilirubin is reduc

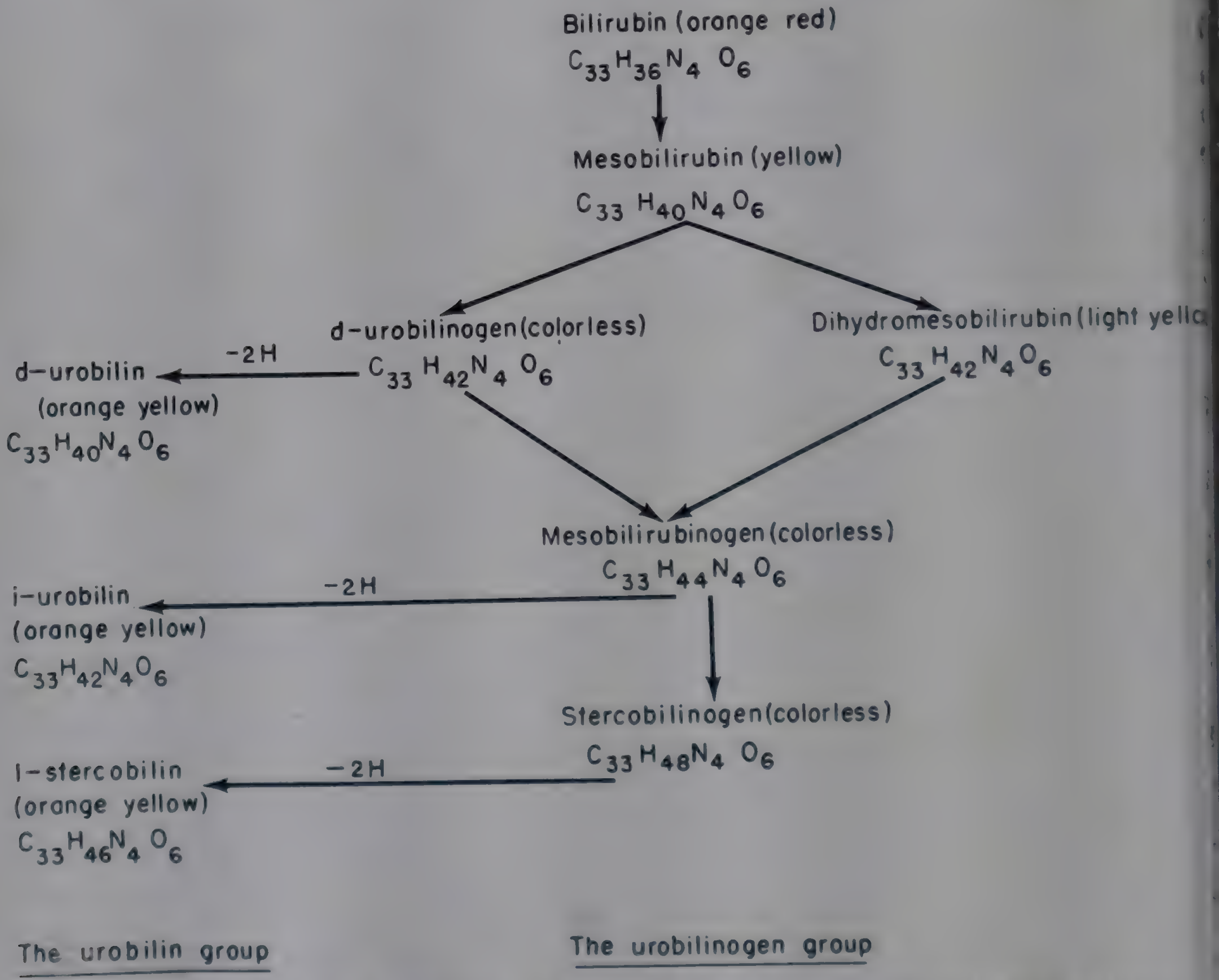
Bilirubin (orange red)
$C_{33}H_{36}N_4O_6$
Mesobilirubin (yellow)
$C_{33}H_{40}N_4O_6$
d-urobilinogen(colorless)
$C_{33}H_{42}N_4O_6$
Dihydromesobilirubin(light yell
$C_{33}H_{42}N_4O_6$
-2H
d-urobilin
(orange yellow)
$C_{33}H_{40}N_4O_6$
Mesobilirubinogen(colorless)
$C_{33}H_{44}N_4O_6$
-2H
i-urobilin
(orange yellow)
$C_{33}H_{42}N_4O_6$
Stercobilinogen(colorless)
$C_{33}H_{48}N_4O_6$
-2H
l-stercobilin
(orange yellow)
$C_{33}H_{46}N_4O_6$
The urobilin group
The urobilinogen group

FIG. 49. The bacterial reduction of bilirubin by the human intestinal flora. (Watson, C. J., Lowry, P., Collins, S., Graham, A. and Ziegler, N. R.: Tr. A. Am. Physicians 67:242)

urobilinogens (Fig. 49), which are par-
ly reabsorbed and re-excreted into the
estine (Fig. 50). The urobilinogen group
ludes 3 colorless chromogens character-
d by a strong Ehrlich aldehyde reaction,
tability, and ease of oxidation to 3 corre-
onding orange-yellow pigments which
npose the urobilin group (Fig. 49). It
nains to be determined whether *d*-uro-
inogen is (in part) a normal intermediary
only formed by an abnormal flora such as
t encountered after oral administration of
ıreomycin or Terramycin.[115] Normally,
obilinogen is excreted almost completely in
feces with up to 280 mg. as the normal
ult value, while little or no urobilinogen
to 4 mg.) is excreted in the urine[110]
ring a 24-hour period.

In hemolytic states the capacity of the
er to "clear" the excess bilirubin formed
y be exceeded so that hyperbilirubinemia
the indirect-reacting type occurs. The
reased amounts of urobilinogen which are
med and reabsorbed from the intestine
y prove to be too much for the liver to
excrete, with the result that excessive
ounts appear in the urine.

In parenchymal jaundice increased
ounts of indirect-reacting bilirubin may
ult from impaired ability of the liver to
nvert the indirect to the direct type. In-
ase in the direct-reacting bilirubin in the
od results from intrahepatic obstruction
d is accompanied by bilirubinuria with
ninished amounts of fecal urobilinogen.
the obstruction is relieved, urinary uro-
inogen may appear in excess due to the
nporary disability of the liver to re-
crete it into the bile.

In jaundice due to a tumor's invading or
npressing the common (or hepatic) bile
ct, there is increase in the direct-reacting
irubin with bilirubinuria. As biliary ob-
uction usually is complete, there is virtu-
y no fecal or urinary urobilinogen.[109] In
ses of common duct stone, the obstruc-
n usually is incomplete, and the degree of
irubinemia usually is less than what occurs
cases of neoplastic jaundice. Excess of
obilinogen which accompanies the biliru-
in the urine is a reflection of hepatic
mage secondary to inflammation and
struction.

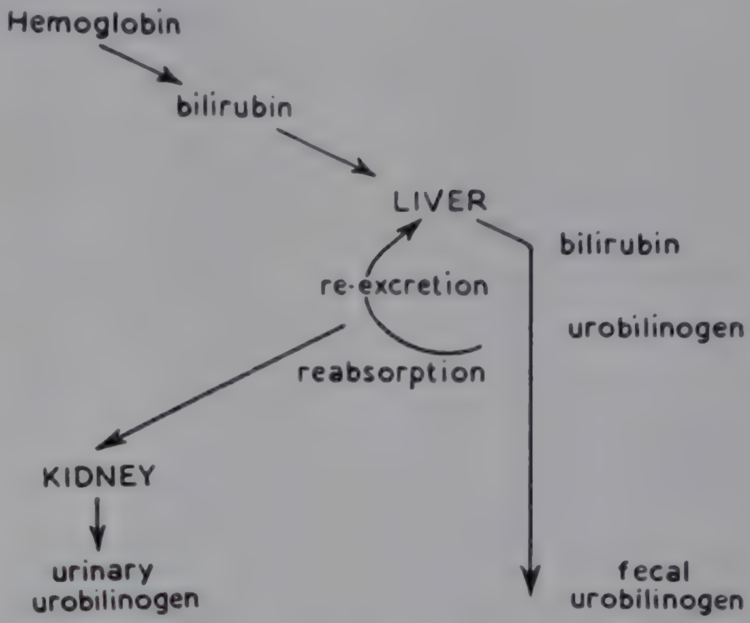

FIG. 50. Fate of bilirubin after excretion into the gut. (Gray, C. H.: The Bile Pigments, Methuen & Co., Ltd., London)

Controversy exists regarding the mechanisms of the development of jaundice.[44] It has generally been accepted that obstructive jaundice is caused by hydrostatic dilatation and rupture of the bile capillaries with leakage of bilirubin back from the biliary system into the lymphatics of the liver and thence to the blood stream. Gonzalez-Oddone observed the prompt appearance of bilirubin (mainly of the prompt-reacting type) in the thoracic duct lymph after ligature of the common duct in dogs. On the other hand, Grafflin and Chaney studied the excretion of fluorescent substances by the liver after ligature of the common duct in white mice and were unable to visualize any suggestion of rupture or leakage of the dye ("and so presumably of bile") into the blood or the lymph. In addition to rupture of bile capillaries secondary to biliary obstruction, various mechanisms have been invoked to explain regurgitation of bile into the blood, particularly in cases of injury to the liver parenchyma. These include (1) increased permeability of the bile capillaries, especially at the ampullae (the point at which the canaliculi emerge from the liver cords),[108] (2) necrosis of liver cells,[93] (3) swelling of the parenchymal cells of the liver with obstruction of the bile canaliculi,[47] (4) swelling of the liver cords, edema of the spaces of Desse and fibrosis of the portal areas,[108] (5) obstruction of the intralobular canaliculi by bile thrombi,[28, 69] and (6) compression or rupture of the canals of Hering in the region of the periportal fields as a result of exudative processes.[101]

McNee classified jaundice into (1) obstructive hepatic, (2) toxic and infective hepatic and (3) hemolytic. Long ago, Budd noted that jaundice may be produced either "by some impediment to the flow of bile to the duodenum and the consequent absorption of the retained bile" or "by defective secretion on the part of the liver so that principles of the bile are not separated from the blood." This distinction is essentially the basis of Rich's classification of jaundice into *retention* and *regurgitation* types. Retention jaundice is due to an overproduction of bilirubin associated with impaired excretion by the liver or, in some instances, to the latter factor alone, resulting in the accumulation of enough bilirubin in the body to stain the tissues. It is synonymous with acholuric jaundice and includes hemolytic jaundice, constitutional hepatic dysfunction (familial nonhemolytic jaundice), and certain cases of isolated hepatocellular injury.

Watson[109] has subdivided regurgitation jaundice into 3 main groups: (1) cancerous, (2) calculous and (3) parenchymal, based largely on the extent of biliary obstruction. He considers biliary obstruction to be complete when the daily fecal excretion of urobilinogen is less than 5 mg. (normal 40 to 280 mg.). He found complete biliary obstruction in 92 per cent of his cancerous cases in contrast with only 3½ per cent of the parenchymal and 11½ per cent of the calculous groups. According to his observations, urobilinogen seldom disappears from the feces for any consecutive 4-day period in parenchymal jaundice, presumably because complete suppression of bile flow for this length of time is relatively rare. Watson's classification has been very helpful in clinical practice.

As a rule, the clinician has little difficulty in distinguishing retention and regurgitation jaundice. His usual task is to determine whether jaundice is due to primary liver disease or to obstruction of the extrahepatic bile ducts by stone or tumor (and in fewer instances by fibrous scar or intrinsic or extrinsic inflammatory swelling). In the differentiation of the various forms of jaundice, he has available 4 methods of approac short of surgical intervention: (1) the h tory and the physical examination, (2) la oratory tests, including the so-called liv function tests, (3) x-ray examination a (4) needle biopsy of the liver in select cases.

CLINICAL EXAMINATION

HISTORY

Occupation. The importance of inquiri into the occupation of a patient with jau dice is evident, with particular reference exposure to hepatotoxic agents. The i creased likelihood of hepatic cirrhosis in ba tenders and brewery workers and the pr disposition to Weil's disease among worke in rat-infested premises are well known.

Recent contact with a jaundiced patie should suggest the possibility of infectio hepatitis. A bout of painless jaundice childhood or early adulthood is due mo commonly to infectious hepatitis which co fers permanent immunity. Therefore, a other episode of jaundice in later years likely to be due to some other cause.

The ingestion or administration of he atotoxic drugs, particularly arsenicals, go salts, sulfonamides, cinchophen or atopha carbon tetrachloride, phosphorus, thorazi and para-aminosalicylic acid may be of eti logic importance. Inquiry should be ma regarding the oral or the sublingual use methyl testosterone. (See Chap. 12, "To Hepatitis.")

Needle puncture from 6 weeks to months prior to the onset of jaundice shou lead to suspicion of homologous serum hep titis. This applies not only to the administr tion of blood plasma and convalescent seru but also to the use of improperly sterili needles and syringes for drawing blood administering parenteral therapy and stylettes for puncturing the finger or the e lobe.

A history of a recent gallbladder oper tion should lead to suspicion of a resid common duct stone or stricture as the ca of icterus, but careful inquiry should made as to the transfusion of blood plasma at the time of surgery in order exclude homologous serum hepatitis.[95] multiple transfusions were given, the like

od of a homologous serum hepatitis be-
nes proportionately increased as it does
the case of pooled plasma.

While **chills and fever** in a jaundiced pa-
nt are usually indicative of cholangitis, it
vell to remember that they may be promi-
nt during the preicteric phase of infectious
atitis. Klatskin believes that a true shak-
chill (with chattering of the teeth) is
gestive of cholangitis, and that chilliness
nore typical of viral hepatitis.[56]

Pruritus. As George Budd pointed out
er a hundred years ago pruritus is most
nounced in cases of occlusion of the com-
n bile duct, particularly by tumor. Itching
often prominent in patients with biliary
rhosis and occasionally occurs in viral
atitis.

Abdominal pain is usually inconspicuous
patients with viral hepatitis who are much
re apt to complain of an uncomfortable
gging or aching sensation in the epigas-
um or the right upper abdomen. In cases
common duct stone the pain generally is
icky and is accompanied by nausea and
niting; usually it requires an opiate for
ief. It need not be confined to the right
per quadrant; frequently, it is located in
epigastrium and occasionally in other
ts of the abdomen. It may be absent, par-
ularly in older individuals.

It is being recognized increasingly that
n occurs in most cases of pancreatic car-
oma. While the nature of the pain is not
thognomonic, it is usually located in the
igastrium and is often described as boring
nature. It frequently radiates to the back.
pointed out by Chauffard, it is worse
en the patient lies on his back and is less-
ed by turning on one side and drawing up
knees, by changing to the prone position,
by sitting up and bending forward. Fre-
ently, it is so severe as to require an opi-
.. The author has observed one patient
h a proved carcinoma of the body of the
ncreas who told him that walking with the
nk flexed afforded him relief. Another
ient with this disease said that he had
tained relief of pain by the use of 2
pirin tablets every 4 hours, day and night,
1 year.

It is important to ask the patient how he
t *before the onset of icterus*. If he experienced anorexia, malaise, nausea, epigastric discomfort, weakness, aches and pains, and fever and chills for about a week or so preceding jaundice, viral hepatitis should be strongly suspected. If he has had symptoms of an abdominal disorder for several months, accompanied by weight loss, a neoplastic process should be considered. If his story is one of upper abdominal discomfort and digestive symptoms of many years' standing, aggravated by the ingestion of fried or fatty foods and accompanied by bloating, belching, heartburn and constipation, common duct stone is apt to be present.

A rapidly developing icterus is usually indicative of parenchymal or hemolytic jaundice.

Color of Urine and Stools. The appearance of dark urine is the best criterion of the onset of jaundice and is apt to precede the yellowish discoloration of the skin or sclerae by one to several days. Reliable information regarding the color of the urine and the stools may be of diagnostic value. In cases of infectious hepatitis the stools are usually clay-colored for a few days to a week or so. In common duct stone they may be alternately acholic and cholic. In neoplastic jaundice they usually remain acholic. The occurrence of brown stools in the presence of deep jaundice is usually indicative of parenchymal jaundice.[120] Although it may prove to be caused by an unsuspected bleeding peptic ulcer, the passage of tarry stools by an icteric patient should suggest carcinoma of the ampulla of Vater or cancer of the pancreas invading the duodenum or the stomach.

PHYSICAL EXAMINATION

Age and Sex. The age and the sex of the patient are of diagnostic help. Infectious hepatitis is seen most commonly in young adults, while common duct stone and neoplastic jaundice usually occur in middle-aged or older individuals. Weil's disease, at least in this country, is said to be rare in females and in children.[8] Portal cirrhosis, hepatoma, pancreatic cancer and primary hemochromatosis predominate in the male, while common duct stone, primary biliary cirrhosis and carcinoma of the gallbladder are more prevalent in the female.

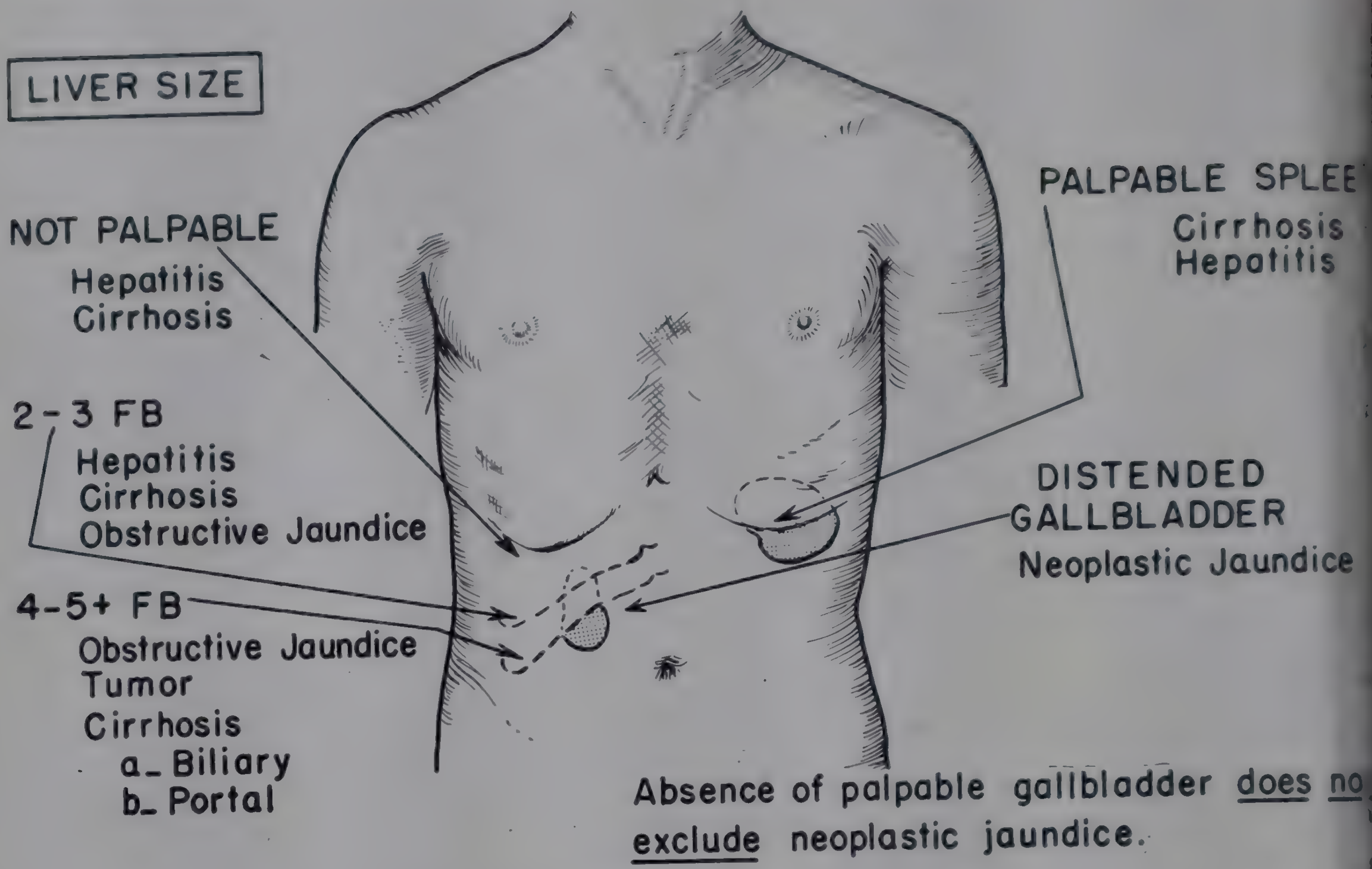
LIVER SIZE
NOT PALPABLE
Hepatitis
Cirrhosis
2-3 FB
Hepatitis
Cirrhosis
Obstructive Jaundice
4-5+ FB
Obstructive Jaundice
Tumor
Cirrhosis
a_ Biliary
b_ Portal
PALPABLE SPLEE
Cirrhosis
Hepatitis
DISTENDED GALLBLADDER
Neoplastic Jaundice
Absence of palpable gallbladder does no
exclude neoplastic jaundice.

FIG. 51. Abdominal findings in various forms of jaundice.

In the physical examination of the jaundiced patient careful search should be made for the presence of *"vascular spiders."*[5, 87] (See Chap. 14 by Patek, p. 441.) They should be looked for carefully with the aid of a good light. Inspection with a hand lens may be necessary to distinguish them from small papular lesions. They may pulsate and can be obliterated by pressing on their central point with the end of a pencil. These structures usually indicate the presence of hepatic cirrhosis, and recent reports would link them with the presence of esophageal varices.[11]

Breath. A peculiar sickly sweetish breath (*hepatic foetor*) is characteristic of severe hepatic disease with necrosis.[111a] According to Hoffbauer, hepatic foetor is detected sometimes on the breath of patients with well-compensated hepatic cirrhosis, or it may follow the therapeutic use of large quantities of pure methionine.

Cervical lymphadenopathy should suggest the presence of viral hepatitis or infectious mononucleosis.

Careful examination of the abdomen is essential to the accurate diagnosis of the cause of jaundice, with particular attentic to the condition of the liver, the gallbladd and the spleen (Fig. 51).

Liver. To obtain a *good feel of the liv* the examiner's hand should be warm, ar the patient should lie on his back, with hea slightly raised, arms at his sides, and kne flexed. After the examiner has placed h hand below the right rib margin, the patie is asked to take a deep breath. The fir "feel" of the liver is often the best, becau flipping the liver edge may be painful ar may keep the patient from taking as full breath subsequently. Sometimes the liver palpated better from one side of the patie than from the other; hence it is best to e amine it from both sides. Sometimes a bett feel is obtained with the patient lying on or side or the other.

Attention should be paid to the size, tl contour and the texture of the organ, to tl presence of tenderness, to the nature of i edge, and to the presence of a perihepat friction rub.

The liver may not extend below the rig costal margin in cases of hepatitis or ci rhosis. Usually it is found from 1 to 2 (c 2 to 3) fingerbreadths below the right cost rgin in viral hepatitis and is frequently der in this disease. A *very large liver* ie extending 4 to 5 fingerbreadths or more ow the right costal margin) is usually in- ative of fatty vacuolization, cirrhosis, nor, amyloidosis or congestive failure. largement of the left lobe of the liver uld suggest hepatic syphilis but may be sed by primary or metastatic tumor or abscess.

The absence of a palpable liver in a pa- nt who has had jaundice for 2 to 3 weeks more would tend to exclude neoplastic truction of the bile ducts, since sufficient stasis should result, by this time, to pro- ce detectable hepatic enlargement.[96] On at st 3 occasions the writer has stood his und successfully on the basis of this sign he face of middle or old age, a liver pro- characteristic of obstructive jaundice and ay changes suggestive of periampullary nor.

A *firm smooth liver* is characteristic of rhosis but may be found in cases of fatty uolization or tumor. A stony-hard, nod- r liver, which is frequently tender, indi- es neoplastic invasion.

The *normal liver* has a sharp edge. A rounded edge was said by the late Horan to be indicative of enlargement.[14]

The wise clinician will attempt to palpate the liver on more than one visit. Differences in the degree of abdominal relaxation, in his own physical state or in the time he devotes to the examination may explain ability to palpate the organ on one day and failure to do so on another.

Gallbladder. The presence of a smooth, nontender, *distended gallbladder* in regurgitation jaundice is almost always indicative of neoplastic obstruction of the common bile duct in accordance with Courvoisier's law. Unfortunately, a distended gallbladder is found much more frequently at operation or necropsy than it is on physical examination. This discrepancy is produced by the overlying right lobe of the liver or, less frequently, by a thick abdominal wall. Failure to detect the presence of a distended gallbladder clinically is therefore of no value in excluding the diagnosis of obstruction or invasion of the common bile duct by tumor. Painless distention of the gallbladder may be encountered in patients who have been vomiting and not ingesting fats.[52]

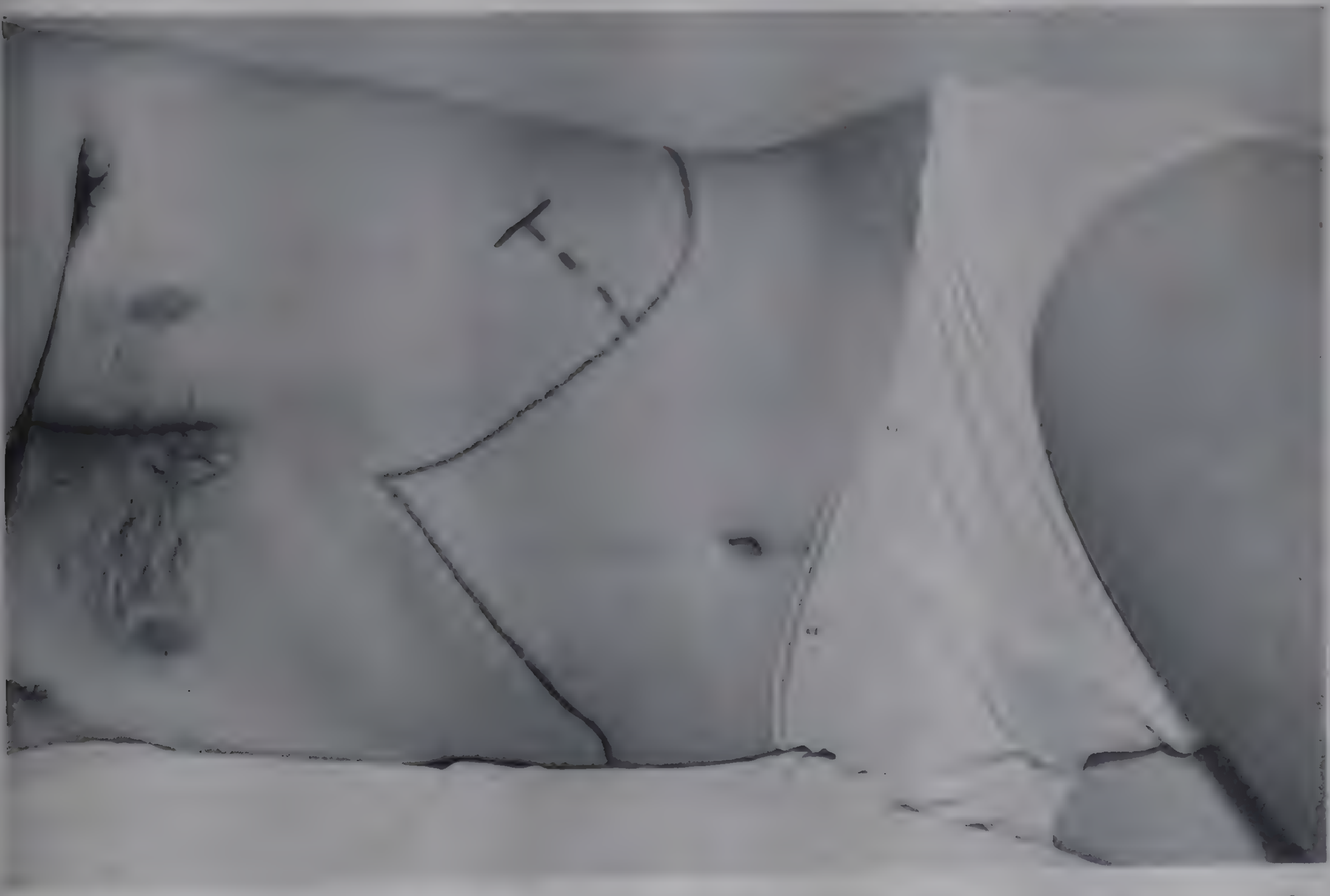

FIG. 52. Normal limits of the upper border of splenic dullness with reference to the costal margin. (Nixon, R. K., Jr.: New England J. Med. 250:166)

Where there has been a difference of clinical opinion regarding the presence of a distended gallbladder or an enlarged liver, on occasions the author has summoned an anesthetist to administer a small dose of Pentothal Sodium intravenously in order to produce satisfactory abdominal relaxation. This procedure has been carried out with the aid of Dr. Adolph Shorr in some 8 or 10 selected instances with gratifying results. Its routine use is not recommended because of the risk of giving barbiturates to patients with liver disease.

Exceptionally, a distended gallbladder may be more visible than palpable. At times it may be found in the right lower abdominal quadrant. Sometimes its long axis lies transversely. As in the case of a palpable liver a distended gallbladder may be detected on one examination and not on another, for the same reasons.

Spleen. Usually the spleen is palpated best with the patient on his right side, with knees bent and left arm extended above the head. One of the examiner's hands should be placed below the left costal margin and the other behind in order to displace the spleen forward. The patient is instructed to breathe deeply, the spleen being felt best at the end of inspiration. In some instances it may be palpated with the patient lying supine with his left arm extending across the back.

Increase in splenic size may be determined also by percussion. Nixon advises that the patient be placed in the right lateral recumbent position with the left arm extended forward and upward, and that percussion be initiated at the lower level of pulmonary resonance in approximately the posterior axillary line and carried downward obliquely toward the lower midanterior costal margin. He finds that the upper border of dullness extends from 6 to 8 cm. above the costal margin, and that dullness increased over 8 cm. is indicative of splenic enlargement in the adult (Fig. 52).

In the absence of hemolytic jaundice a palpable spleen usually is indicative of parenchymal jaundice. The spleen is palpable in about one half of patients with hepatic cirrhosis and in about 10 per cent of patients with viral hepatitis, It is well to bear in mind that in obstructive jaundice of long standing splenomegaly may be a manifestation obstructive cirrhosis. In cancer of the bo and the tail of the pancreas splenic enlarg ment may result from encroachment of t tumor on the splenic vein.[27]

Palmar Erythema. Patek and Perera ha pointed out the frequency of a symmetr erythema, so-called palmar erythema, i volving the eminences of the palms and t digits of the hands in patients with hepa cirrhosis.

Ascites. The presence of ascites in a jau diced patient usually is indicative of hepa cirrhosis but may be observed in fatal very severe cases of hepatitis, in the presen of peritoneal tumor implants or followi invasion of the portal vein by tumor.

Prominent superficial abdominal veins a observed most often in patients with hepa cirrhosis but may occur in the presence peritoneal tumor implants, obstruction the portal vein by tumor or in cases of i ferior caval obstruction. In portal hyperte sion the blood flow in the abdominal vei is radially away from the umbilicus, where in inferior caval obstruction it is always u ward over the abdominal wall.[100]

Miscellaneous findings include the pre ence of an abdominal mass, usually indic tive of intra-abdominal tumor. Absence axillary or pectoral hair is suggestive of c rhosis of the liver, as are testicular atrop and gynecomastia, although the last tv have been reported in hepatitis.[58] The pre ence of multiple venous thrombi in a jau diced patient should suggest cancer of t body or the tail of the pancreas.[54]

LABORATORY TESTS

Laboratory tests are of value in disti guishing (1) retention from regurgitatio jaundice, (2) parenchymal from obstructi jaundice and (3) jaundice due to comm duct stone from that due to neoplasm. Th are of less help in differentiating the chi forms of parenchymal jaundice, namel hepatitis from cirrhosis.

Routine Tests

1. Blood Count. According to Havens, the white cell count usually is reduced du ing the preicteric and normal during th ric phase of infectious hepatitis, although es and Minot reported leukocytosis nin the first few days of the disease. The ef value of a white cell count in a patient n jaundice is in ruling out uncomplicated l hepatitis by the presence of leukocyto- which is found frequently in toxic hepa- , amebic hepatitis, metastatic hepatic plasm, common duct stone (with cho- gitis) and Weil's disease. In the absence lood loss the presence of anemia should gest a hemolytic process, as should the ling of reticulocytosis and spherocytosis.

. **Blood Urea Nitrogen.** Elevation of the od urea nitrogen in a patient with jaun- e should suggest the possibility of Weil's ease or exposure to a hepatotoxic agent ch is also injurious to the kidney, such, example, as carbon tetrachloride.

. **Urine Analysis.** The presence of albu- uria should suggest the possibility of il's disease, although it may occur in the icteric and the early icteric phases of l hepatitis.

LIVER PROFILE

As Hanger[44] has well put it, "Each clinic tinues to employ a preferred battery of s, but there is increasing unanimity as to ch ought to be included in routine in- tigations. Standardization of methods, vever, has not kept pace, and case reports tinue in part to be valueless unless the nniques employed and the normal range each determination are specifically ed."

or a number of years the writer and his ociates have employed the following pro- in the differential diagnosis of jaundice: serum bilirubin (method of Malloy and Evelyn as modified by Ducci and Watson; upper limit for 1-minute bilirubin, 0.25 mg. per cent, and for total bilirubin, 1.50 mg. per cent[125, 126]); (2) cephalin-cholesterol flocculation (method of Hanger;[42] 1 to 2+ in 24 hours considered normal); (3) thymol turbidity (Shank and Hoagland's modification[98] of Maclagan's method,[71] with normal range of 0 to 5 units); (4) zinc sulfate turbidity (method of Kunkel, with normal values of 12 units or less); (5) thymol flocculation (Neefe; 1+ flocculation considered normal); (6) serum alkaline phosphatase (Bodansky method, with normal for adults 0 to 4 units).

LIVER PROFILE IN MEDICAL JAUNDICE

			Hepatitis
Ceph. Floc.	3-4+	(24 hrs.)	– 80%
Thymol Turb.	>6	($BaSO_4$)	– 70%+
$ZnSO_4$ Turb.	>12		– 88%
S.Alk.Phos.	<10 B.U. % <30 K.A.%		– 92%

FIGURE 53

In parenchymal jaundice there usually are a positive cephalin-cholesterol flocculation, increased thymol and zinc turbidity, positive thymol flocculation, and little or no increase in the serum alkaline phosphatase (less than 10 Bodansky units or 30 to 35 King-Armstrong units) (Fig. 53). On the other hand, the usual findings in cases of obstructive jaundice are a negative cephalin-cholesterol flocculation, normal thymol and zinc turbidity, negative (or 1+) thymol flocculation and increase in the serum alkaline phos-

LIVER PROFILE IN
COMMON DUCT STONE VS NEOPLASTIC JAUNDICE

		Per cent Stone		Per cent Tumor
Prompt S. Bil	<10 mg.%	87	>10 mg.%	81
Neg. Ceph. Floc.		57		89
Normal T.T.		75		92
S.A.P.	>10 B.U.	63		90

FIGURE 54

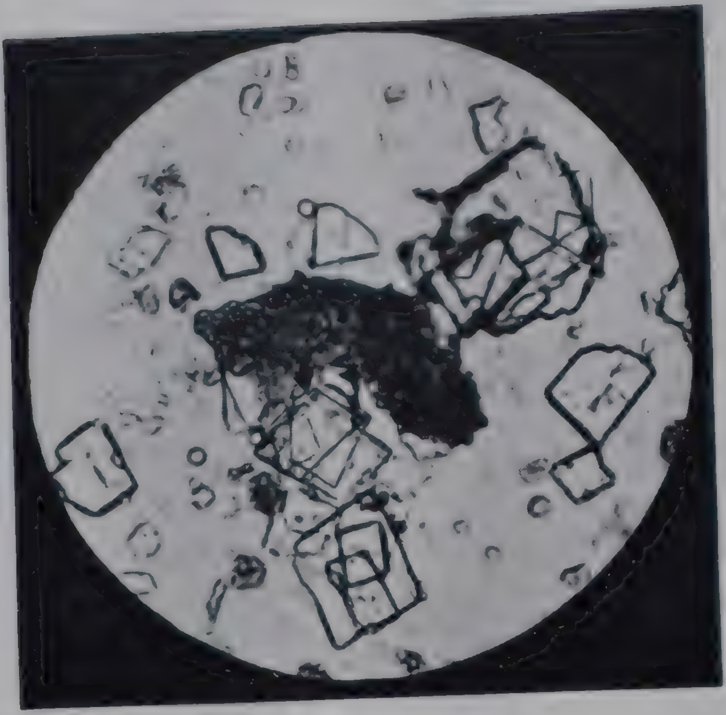

FIG. 55. Combination of cholesterin and calcium bilirubinate crystals is pathognomonic for stones (× 360). (Lyon, B. B. V.: Atlas on Biliary Drainage Microscopy, privately printed)

phatase of more than 10 Bodansky units (or more than 30 to 35 King-Armstrong units). According to Hanger,[44] a negative cephalin flocculation test combined with rising serum alkaline phosphatase and deepening jaundice comprises the most accurate index of obstructive jaundice.

The "liver profile" may be of further aid in differentiating cases of common duct stone from neoplastic obstruction. The concentration of prompt-reacting serum bilirubin usually is less than 10 mg. per cent in patients with common duct stone but usually exceeds this level in patients with neoplastic jaundice. Likewise, the serum alkaline phosphatase is increased relatively less in cases of common duct stone. The cephalin flocculation is more frequently negative, and the thymol turbidity more frequently normal in patients with neoplastic jaundice (Fig. 54). The higher levels of serum bilirubin and serum alkaline phosphatase in patients with neoplastic jaundice, as compared with patients with common duct stone, can be explained by the more nearly complete and more persistent biliary obstruction in the cases with tumor. The more frequent occurrence of a positive cephalin flocculation and increased thymol turbidity in patients with common duct stone is a reflect
higher incidence of cholangitis
ondary hepatitis.

It is well recognized that most
dividual laboratory tests consti
so-called "liver profile" are not s
function tests and hence may be
the absence of liver disease. The
of the clinical examination in th
tation of the results of these liv
tests becomes evident. As Him
stated so well, "There is yet no
approaches in value a careful
sessment of the patient and n
can be interpreted without it." T
exemplified by increases in the s
line phosphatase which occur in t
of osseous lesions such as Pag
and hyperparathyroidism and
cephalin flocculation tests observ
tious mononucleosis, hemolytic
disseminated lupus erythemato
cious anemia, acute leukemi
malaria, and diffuse diseases of t
endothelial system.[44]

Also, it is known that no si
function" test or combination of
formly positive or negative in
forms of jaundice. For example,
lin-cholesterol flocculation is
about 80 per cent[80] to 90 per cen
of viral hepatitis and in about 8
of cases of toxic hepatitis.[44] A c
of the thymol flocculation and s
line phosphatase gives useful in
the type of jaundice in about 80
cases (Maclagan, see p. 147).

DUODENAL DRAINAGE

Duodenal drainage may be val
differential diagnosis of jaundic
helping to confirm or disprove t
of biliary obstruction, (2) by fur
terial that can be tested for its
pancreatic enzymes, (3) by yieldi
for cytologic examination, (4)
strating the presence of gross b
duodenal contents, which is stron
tive of ulcerating tumor of the
Vater,[20] and (5) by furnishing
cholelithiasis in the form of calci
nate and cholesterol crystals (se
In cases of common duct stone, t

sually contain bile and a normal
pancreatic enzymes. In carcinoma
d of the pancreas both bile and
enzymes are almost always dimin-
ntirely absent. In carcinoma of the
bile duct which does not involve
eatic duct, bile is absent, but pan-
zymes may be present in normal
ion. While the results of the pan-
ction tests depend on the patency
natomy of the ducts in patients
noma of the ampulla of Vater,[4]
ly is absent, and the pancreatic
re diminished or absent.[119]

ain duodenal contents for pancre-
me determinations the use of a
nen tube for separate aspiration of
ch and the duodenum is advisable
prevent acidification and destruc-
e pancreatic enzymes. The pH of
nens used should be above 7. For
ic of testing external pancreatic
he reader is referred to the works
oef and Bauman.

and Byrnes have emphasized re-
value of cytologic examination of
ents of duodenal aspiration in tu-
the gallbladder, the extrahepatic
and the pancreas (Fig. 56). They
he following procedure:

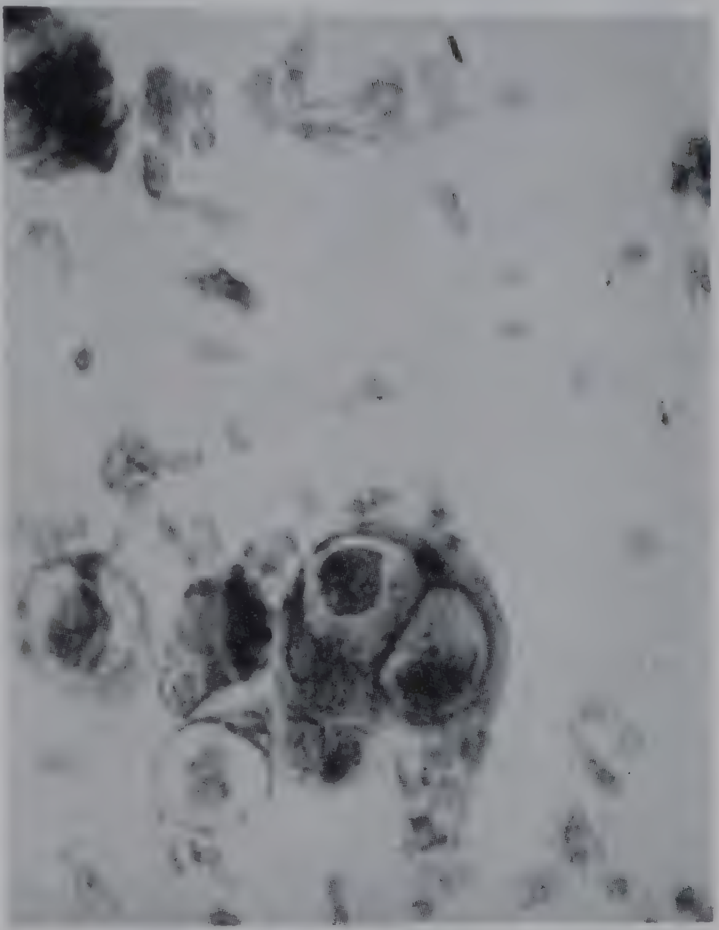

FIG. 56. One of many clumps of neoplastic cells surrounded by tall columnar normal epithelial cells, found in duodenal sediment of patient with carcinoma of head of pancreas, pathologically reported as resembling hepatoma (× 800). (Lemon, H. M., and Byrnes, W. W.: J.A.M.A. **141**:254)

thod of obtaining duodenal contents
widely accepted methods of duodenal
using either a Levin or a Rehfuss
flow of bile and pancreatic juice has
ases been stimulated with administra-
33.3 per cent solution of magnesium
cretin or methacholine chloride, but
t imperative for success. The tube
be lubricated with oil at any time.
py has been used in most instances to
the location of the tip of the tube.
of fasting gastric juice and A, B
e are separately collected in recep-
lled in an ice bath. The fluid is
neutralized to pH 7 and centrifuged
evolutions per minute for ten minutes.
nent from specimens containing as
to 3 cc. of secretion may be used for
nears on a similar number of slides,
usually one to three slides are made
15 cc. of fluid obtained. The smears
iment are then fixed while moist for
e-half hour in chilled acetone, after
y are dipped twice in a 1 per cent solution of celloidin in acetone, allowed to drain 10 to 15 seconds in air and then are transferred to 95 per cent alcohol. This celloidin jacket is necessary to insure good adhesion of the smeared cells to the slides during the staining process, which is carried out using the method described by Papanicolaou.

ROENTGEN EXAMINATION

X-ray examination has been of limited value in the differential diagnosis of jaundice, due largely to 4 factors: (1) inability to furnish direct evidence of hepatitis, (2) inadequacies of present-day technics in the demonstration of tumors producing jaundice, (3) limitations of cholecystography and intravenous cholangiography, and (4) lack of proof that gallstones are the cause of jaundice by their mere demonstration.

X-ray changes caused by tumors produc-

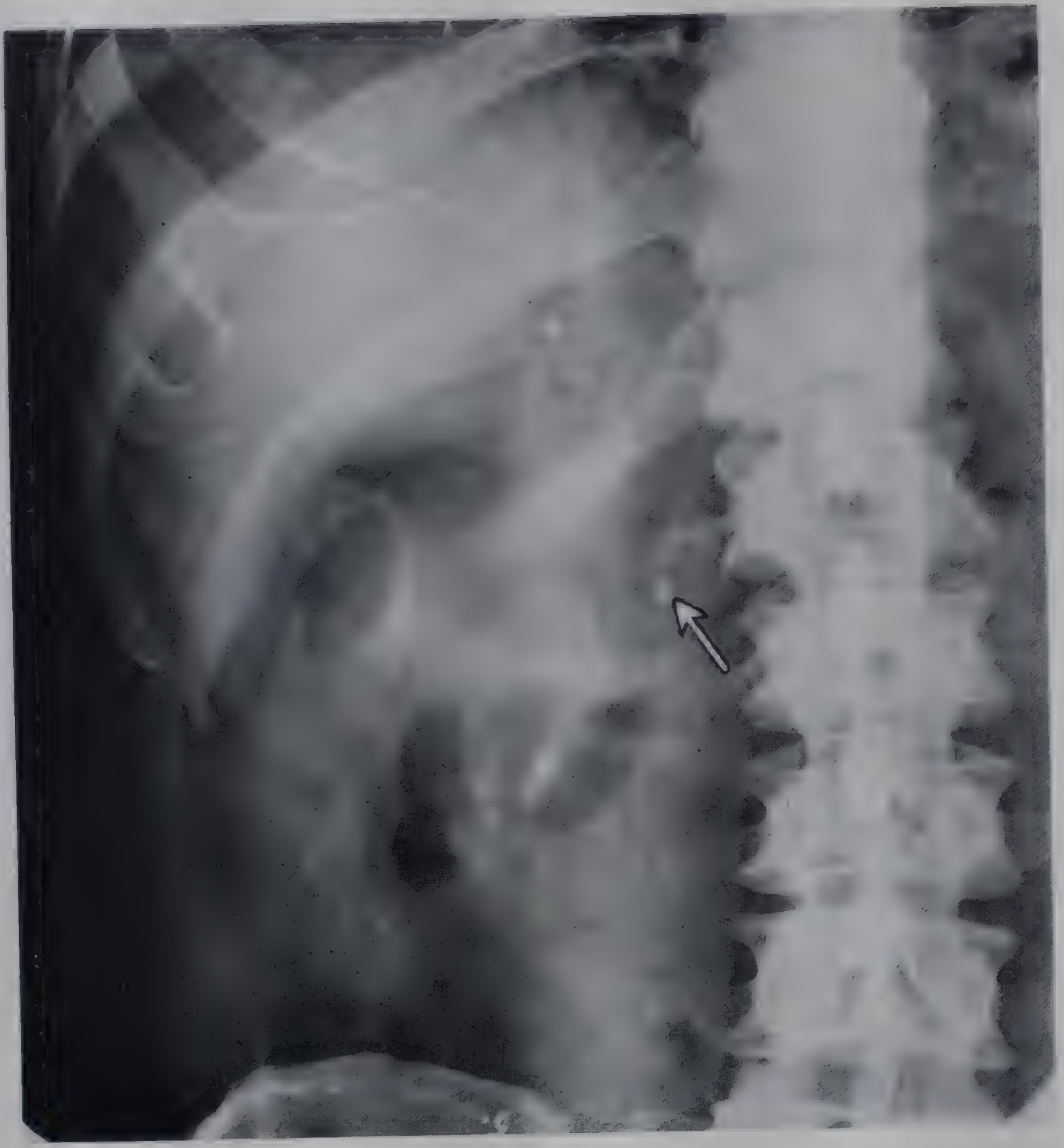

Fig. 57. O.S. 818 49. Stone in common duct (indicate by arrow) with second stone in th region of the gallbladder. (Schiff, L. Clinical Approach t Jaundice, Springfield, Ill., Thomas)

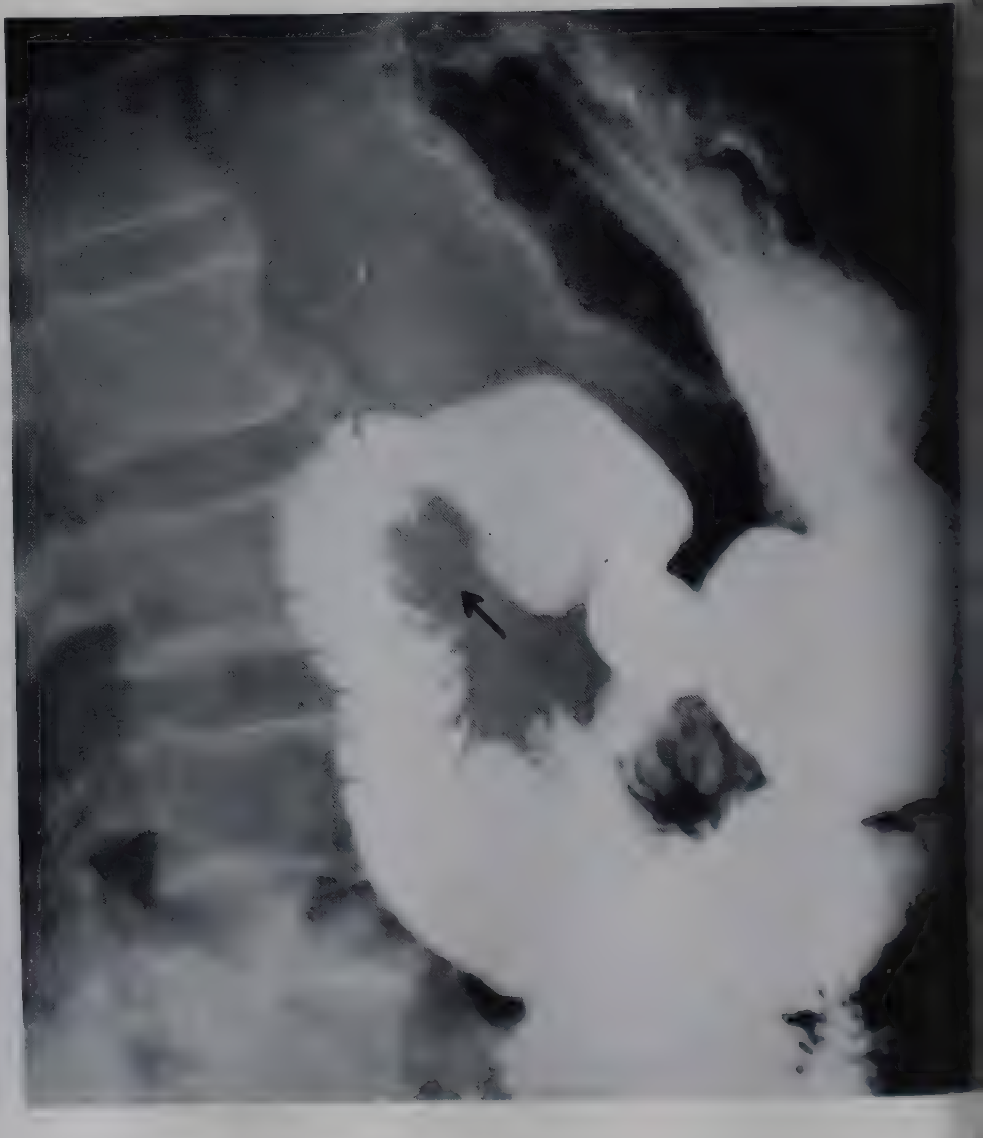

Fig. 58. J.A. 172320. Carcinoma of pancreas. Note defect on anteromesial border of proximal descending duodenum (arrow).

icterus depend largely on effects on con- ous structures resulting from expansion the neoplasm and may not be present ing the early stages of tumor growth. A cinoma of the head of the pancreas pro- ing jaundice may not be large enough to ge appreciably on the surface of the gland therefore may escape detection on roent- examination.

Cholecystography has been of little diag- tic value in cases of regurgitation jaun- e, since the gallbladder may fail to ualize because of the liver's impaired abil- to excrete the dye. Visualization of the bladder has been reported, however, in presence of an icterus index of 66 and) by Jacobi and Ottenberg, respectively. cently, Readinger and associates have wn that when the total serum bilirubin ess than 11 mg. per cent and the retention bromsulphalein less than 30 per cent a ge proportion of patients with mild hepa- s are able to excrete Priodax and concen- e it in the gallbladder well enough to ct visualization by roentgenogram. They sider it advisable to give a double dose the radiopaque dye orally (12 Priodax lets) when the total serum bilirubin is ve 5 mg. per cent or when the brom- phalein retention exceeds 15 per cent. e fear that the dye may harm the jaun- ed patient has long been dispelled by the erimental observations of Walsh and Ivy l by clinical experience. The demonstra- n of gallstones by x-ray examination does indicate that they are the cause of jaun- e, since they occur frequently in cases of cinoma of the gallbladder, the ampulla Vater and the bile ducts and occasionally coincidental in patients with pancreatic cer, hepatic cirrhosis, or acute hepatitis.

Despite its limitations, the roentgen exami- ion may be helpful in the diagnosis of the se of jaundice. A plain film may reveal argement of the liver and the spleen, a ne in the common bile duct (Fig. 57), a und-glass appearance suggestive of ites, or an elevated right diaphragm in- ative of hepatic tumor or abscess. Esoph- al varices may be visualized in cases of atic cirrhosis or hepatoma (see Chap. 8, rtal Hypertension"). By revealing the sence of a primary neoplasm in the ali-

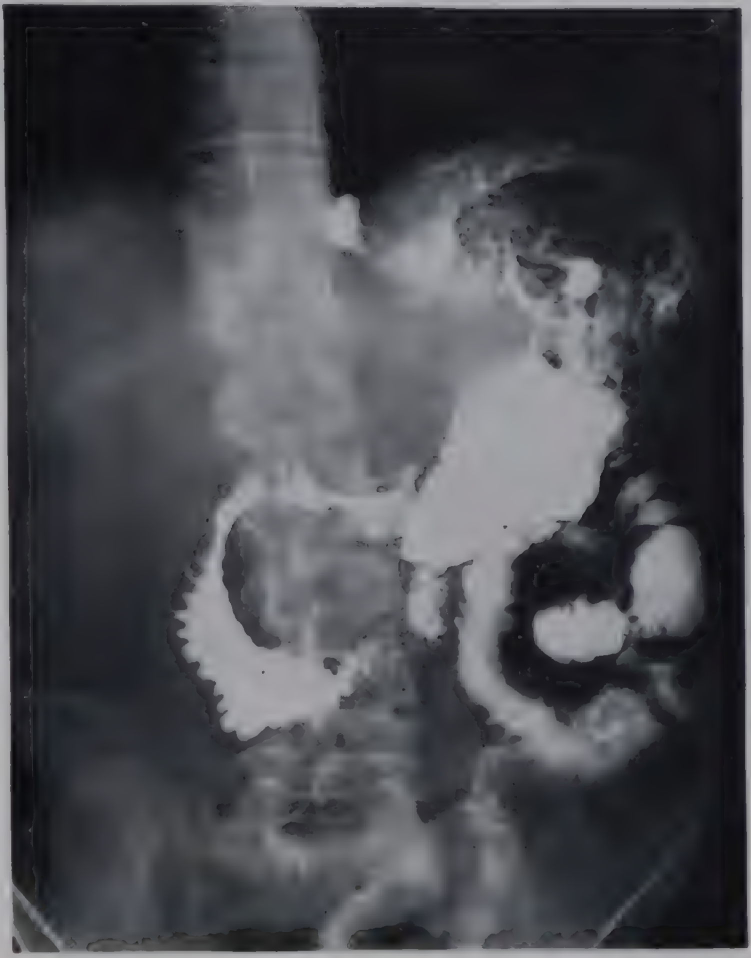

Fig. 59. P.M. Carcinoma of the head of the pancreas, producing extrinsic pressure on bulb and smoothing of inner border of duodenum. (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

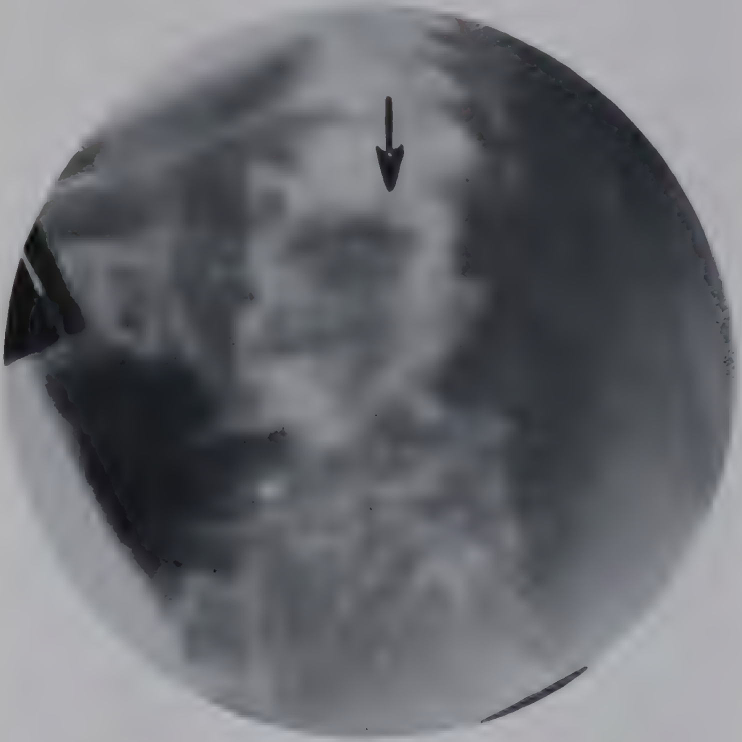

Fig. 60. R.R. 32331. Carcinoma of the ampulla of Vater. Spot film showing defect in descending duodenum. (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

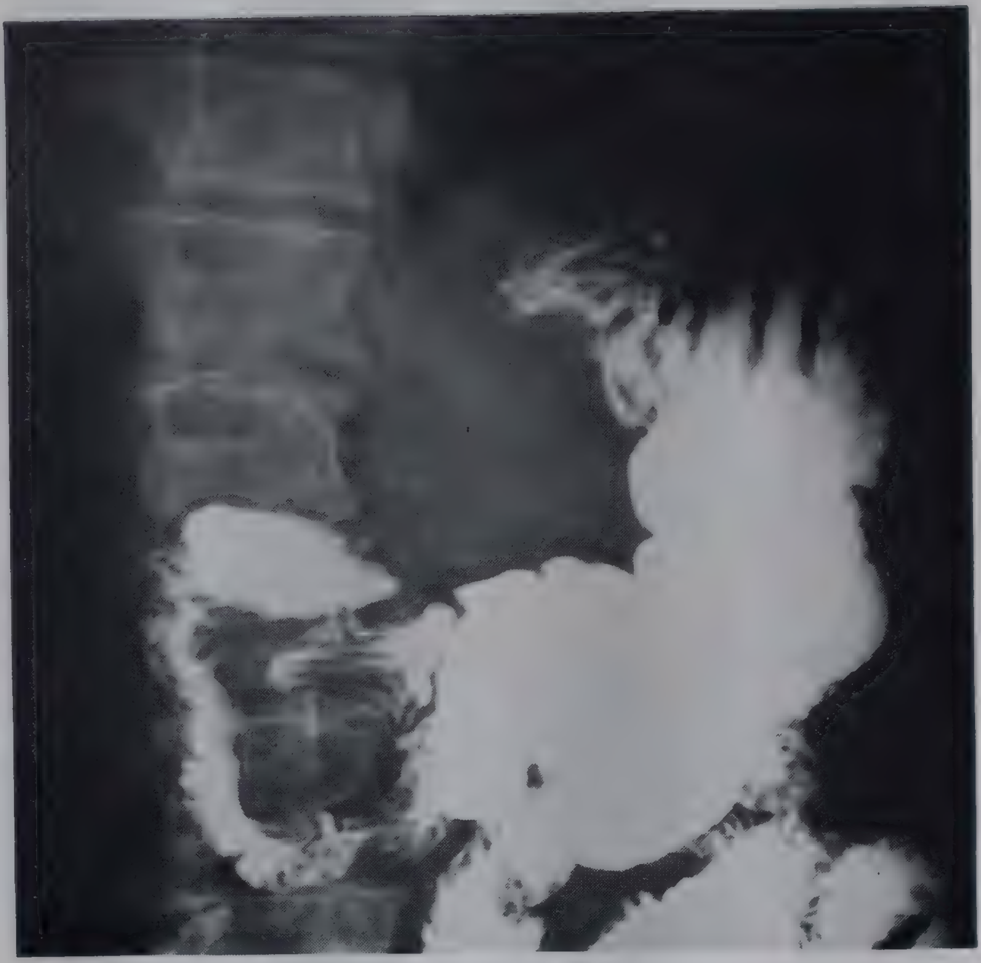

Fig. 61. W.B. 539. R versed-3 sign in the descen ing portion of the duodenu with clinical evidence su gestive of carcinoma of th ampulla of Vater. (Schiff, L Differential Diagnosis Jaundice, Chicago, Yr. B Pub.)

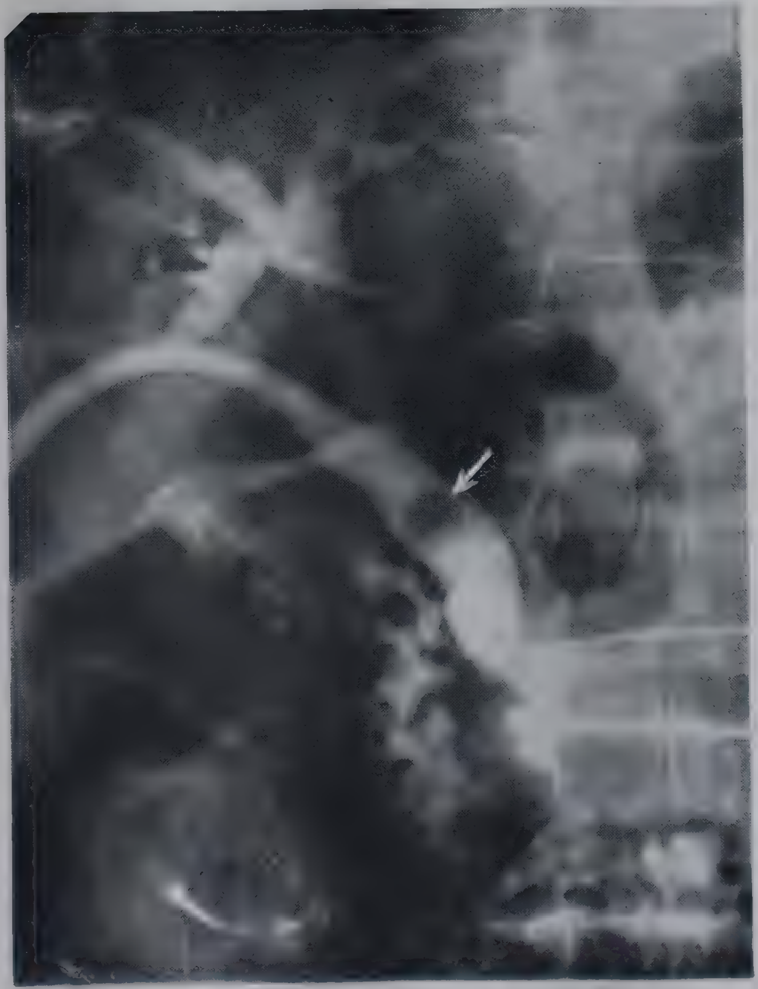

Fig. 62. W.J. Operative cholangiogram showing common duct stone. (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

mentary canal or other body system, th roentgen examination may help to confirm the diagnosis of a metastatic hepatic tumor or, by failing to reveal a primary site elsewhere, it may strengthen the clinical impression of hepatoma. It may furnish evidence of an enlarged liver by demonstratin displacement of the stomach posteriorl and/or to the left, or displacement of th hepatic flexure of the colon downward.

A pancreatic tumor may produce anterio displacement of the duodenal loop, downward displacement of the duodenal-jejuna juncture, compression or invasion of th duodenum or the stomach or widening of th duodenal loop (Figs. 58, 59). Periampullar tumor may produce a filling defect in th descending duodenum (Fig. 60) or Frostberg's reversed-3 sign (Fig. 61).

By demonstrating calcification in the pancreas the roentgen examination may lead t the diagnosis of relapsing pancreatitis as cause of icterus.

The importance of operative and postoperative cholangiography in the detection of stones in the common and the intrahepatic ducts is well known (Figs. 62, 63) It has been estimated that common duc

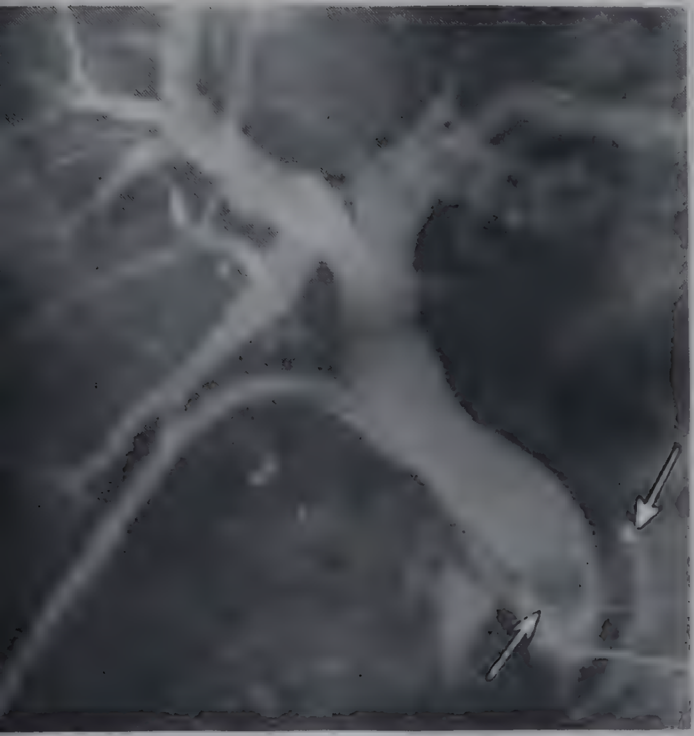

FIG. 63. W.deJ. Note shift of stone on comparing with Figure 62. Upper arrow points to pancreatic duct. (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

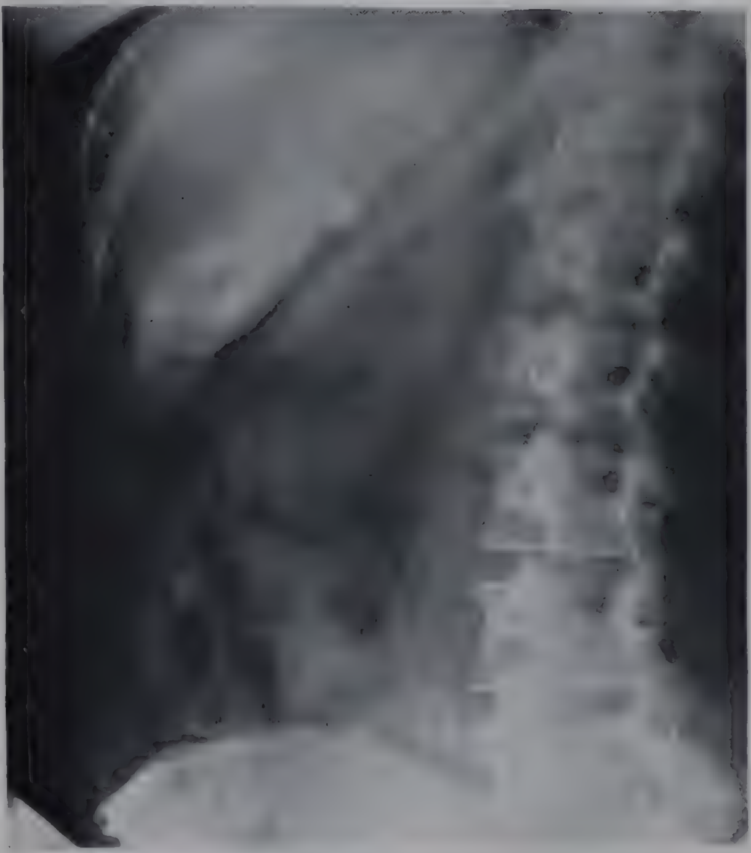

FIG. 64. M.B. 201236. Recurrent pancreatitis. Normal gallbladder and common duct. Film made 30 minutes after 40 cc. of cholegrafin had been injected intravenously.

culi may be overlooked by ordinary meth- in between 10 and 30 per cent of oper- d cases. The necessity for meticulous hnic and intimate teamwork on the part he anesthetist, the roentgenologist and the geon has been stressed. For details the der is referred to the monographs of rizzi, Norman, and Partington and Sachs.

At the time of cholecystography, the ex- hepatic ducts may be demonstrated by ns taken at frequent intervals following a y meal.[12, 94, 103] By this means the trans- odenal segment of the common duct may visualized.[94] Visualization of the extra- atic ducts by means of “oral cholecystog- hy” in patients who previously have dergone cholecystectomy has been re- ted.[105] The value of this method proba- will be limited in patients with jaundice. cently, there has been developed a method visualizing the gallbladder and the extra- atic ducts following intravenous injec- n of a new iodine-containing compound 4% iodine), cholegraphin.[6, 29, 30, 49, 62, 70, 91] The bile ducts visualize optimally at 30 nutes, while optimal gallbladder visualiza- n occurs usually at 2 to 2½ hours. This thod is equally applicable to patients with rmal, diseased or resected gallbladders. Reactions are reported to be few. Since visualization of the bile ducts depends upon the fact that 90 per cent of the dye is secreted actively by the liver cells (and 10% by the kidneys), impairment of the excretory function of the liver that is apt to be present in regurgitation jaundice limits the applicability of the test to the icteric patient. Through the courtesy of Dr. Mark H. Lund of the Squibb Institute for Medical Research, the author and his associates,[123] at the time of this writing, have used the test in 30 patients and have been much impressed with its possibilities (Figs. 64-66) when jaundice is very mild (serum bilirubin less than 4 mg. per cent).

NEEDLE BIOPSY OF THE LIVER

The use of needle biopsy of the liver should be confined to selected cases of jaundice. In the first place, it has been estimated that the diagnosis of the cause of jaundice can be made in from 85 to 90 per cent of cases on the basis of the clinical examination and the results of laboratory tests.[43, 111]

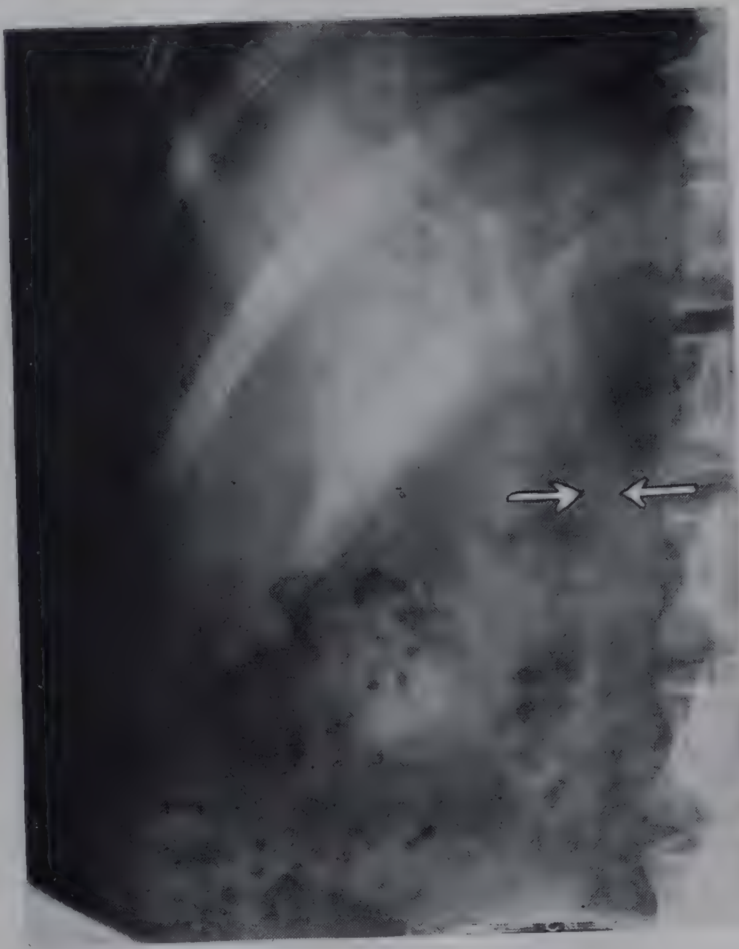

FIG. 65. R.B. (J.H. 44800). Common duct stone. Note dilatation of common duct (arrows) and main hepatic ducts. The stone is not visualized. Film made 30 minutes after 40 cc. of cholegrafin had been injected intravenously.

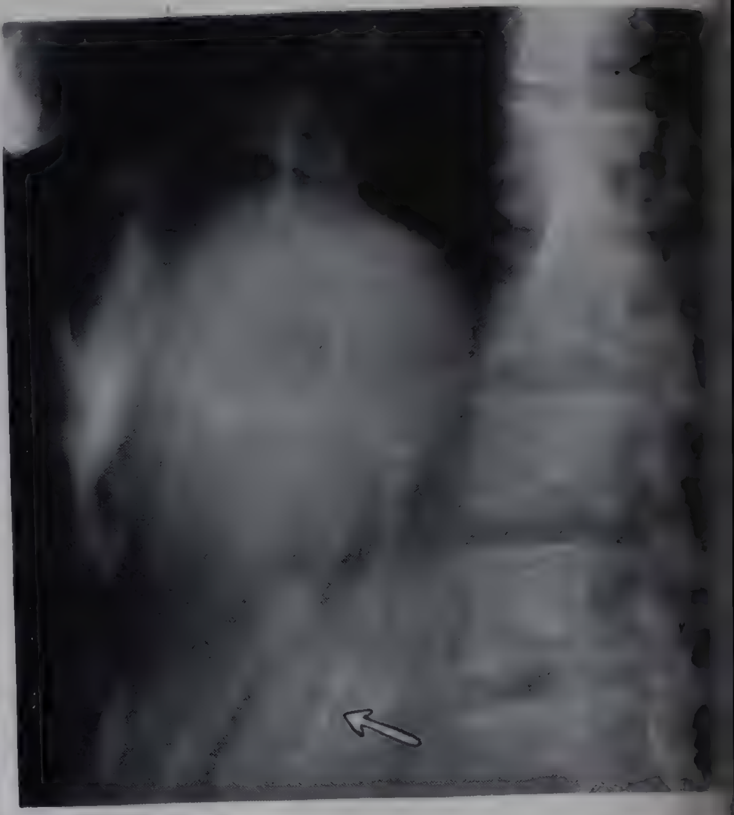

FIG. 66. M.J. (J.H. 71720). Possible common duct stone, showing dilated common bile duct (proved at operation). Note pyelogram (arrow). Film made 45 minutes after 60 cc. of cholegrafin had been injected intravenously.

Second, there is the added danger of hemorrhage and, in cases of obstructive jaundice, bile peritonitis.[34] Nevertheless, in carefully selected patients who are observed closely after the procedure and treated promptly when indications arise, the danger is small. The over-all risk of needle biopsy of the liver includes a mortality of 0.1 per cent and a complication rate of 0.32 per cent, according to the recent reviews of Terry and Zamcheck and Klausenstock. In 1949 my associates and I reported the use of needle biopsy in 157 cases of jaundice, 30 of which were obstructive jaundice, without a serious complication.[116] Sheila Sherlock reported a similar experience in a similar number of cases.[99]

It is the writer's belief, based on an experience of over 10 years, that needle biopsy of the liver is indicated in the jaundiced patient in the following 5 situations:

1. When difficulty exists in distinguishing medical from surgical cases. Needless surgery may be averted by demonstrating presence of hepatitis; conversely, surgi therapy may be expedited in cases of structive jaundice.

It should be emphasized that the bio specimen is almost always of no help determining the cause of extrahepatic struction; hence, needle biopsy of the li should not be performed when the jaunc obviously is due to extrahepatic obstr tion! Instead, surgery should be carried promptly.

2. History of exposure to a known hepa toxic agent. The author has seen a num of instances in which a patient exposed t known hepatotoxic agent was found to suffering from viral hepatitis. With recov from the hepatitis the patient was permit to return to his occupation. In a tubercul patient who became jaundiced while rece ing para-aminosalicylic acid, resumption the drug was advised when it was fou that the icterus was due to viral rather th toxic hepatitis.

3. The presence of an obscure syste disorder. Unsuspected granulomatous may be revealed in the biopsy specimen.

. **Suspicion of metastatic neoplasm of the** . In over 100 cases of proved neoplasm ne liver the needle specimens were posi- for tumor in 74 per cent; and, interest- y enough, the positive incidence was as with the transthoracic as with the sabdominal approach.[107]

. **Hepatomegaly of undetermined cause.** atty liver may be discovered in a patient ight to have cirrhosis, neoplasm or hepa- . Histologic changes of obstructive jaun- may be found in patients with suspected atitis, and vice versa.

leedle biopsy of the liver is of great value istinguishing hepatitis from cirrhosis, the y from the cirrhotic liver, viral from toxic atitis, and cirrhosis from malignant neo- m. On the other hand, occasionally it y prove to be quite disappointing. It may of no value in distinguishing obstructive ndice due to tumor from that due to ne. Laboratory tests are much more help- in this connection.

n the past the writer and his associates e attained a diagnostic accuracy of 92 cent with the combined use of needle psy, clinical and laboratory examinations cases of jaundice.[97] Bjørneboe and his ciates have reported a diagnostic ac- acy of 98.5 per cent in a group of pa- ts which included many without jaundice. the technic of the procedure and for changes revealed in the various disorders sing jaundice, the reader is referred to Chapter by Schiff and Gall on "Needle psy of the Liver," and Chapter 10 by etana on "Pathology of Hepatitis."

PITFALLS IN DIAGNOSIS

MISCELLANEOUS

number of factors may mislead the ician in his quest for the cause of jaun- e. A *history of alcoholism* may lead him suspect hepatic cirrhosis in a patient ose liver proves to be normal or the seat some other disorder. The *age of the pa- t* may be misleading. Viral hepatitis, par- larly homologous serum hepatitis, is not ommon in the older age group (see efe, p. 311), and young adulthood does necessarily exclude neoplasm. In the past year the writer has seen 2 proved cases of carcinoma of the bile ducts in individuals in their early thirties, and he recalls a case of carcinoma of the periampullary region in an individual aged 28 and one of carcinoma of the pancreas at 24. *Prominent weight loss* strongly suggests neoplasm as the cause of jaundice; however, such loss may occur in severe cases of hepatitis as a result of marked anorexia and in cases of common duct stone because of nausea and vomiting.

A *history of tumor resection* preceding jaundice should suggest the presence of metastatic neoplasm of the liver. In some instances the clinician may be surprised to find that he is dealing with an homologous serum hepatitis secondary to blood or plasma administered at the time of operation. The writer recalls a patient who had received blood to combat shock resulting from multiple fractures, and several months later he became jaundiced and was found to be suffering with a carcinoma of the rectum. Metastatic neoplasm of the liver was strongly considered, but further study including needle biopsy of the liver revealed the jaundice to be due to viral hepatitis.

The writer has been impressed with the *frequency of painless jaundice in elderly individuals suffering with common duct stone*. Variations in the color of the urine and the stools over a period of time may be an important diagnostic clue. In cases with very mild or receding jaundice the use of intravenous cholangiography holds great promise.

Obstructive cirrhosis may be mistaken for hepatitis or portal cirrhosis. Laboratory tests in keeping with obstructive jaundice, the prolonged duration of jaundice, and the results of x-ray studies may put the clinician on the right track. Duff has pointed out that splenomegaly may be produced by encroachment of carcinoma of the body of the pancreas on the splenic vein. The writer has observed a patient with obstructive cirrhosis secondary to a carcinoma of the ampulla of Vater in whom splenomegaly and hepatomegaly preceded marked icterus by many months.

Focusing too much attention on the icterus may be responsible for *overlooking the pallor* of hemolytic jaundice.

Unusually prolonged jaundice does not necessarily exclude neoplasm as the cause. The writer has seen a patient with proved carcinoma of the ampulla of Vater with a history of 18 months' duration and one with carcinoma of the bile ducts in whom jaundice lasted for 3 years.

CONSTITUTIONAL HEPATIC DYSFUNCTION

Constitutional hepatic dysfunction (familial nonhemolytic jaundice) is a disorder that still is not adequately recognized.[18, 22] Since it is most common in young adults it is apt to be mistaken and treated for viral hepatitis. The writer has seen 3 patients with this disease who were confined to bed unnecessarily for periods of time. One of them was a hospital laboratory technician who had been handling blood sera and was assumed to have acquired hepatitis as a result of her occupation.

The serum bilirubin determination is of the greatest help in the recognition of this disorder in that the increase in bilirubin is almost entirely of the indirect type. This is in sharp contrast with the increase in the prompt-reacting or 1-minute bilirubin that occurs in hepatitis. The total bilirubin usually is under 5 mg. per cent but may range from 2 to 15 mg. per cent.[19] There is almost always no bilirubin in the urine, and the amount of urobilinogen in the stools is normal or decreased. A history of chronic fluctuating icterus of a mild degree, together with intermittent fatigue accompanying exacerbations of the icterus, absence of hepatomegaly or splenic enlargement, and lack of corroborative evidence of hemolytic jaundice or viral hepatitis should aid in the recognition of this disorder. Liver biopsies have been reported as normal[21, 59] or revealing slight degrees of fatty vacuolization.[50]

JAUNDICE FOLLOWING ORAL METHYL TESTOSTERONE THERAPY

Of much interest is the occurrence of jaundice in patients receiving oral methyl testosterone.[2, 9, 10, 55, 117, 118] (See also p.369, Chap. 12, by Klatskin.) The icterus usually appears from 3 to 4 months after the drug has been started, although it may occur within 8 days after therapy has begun.[118] The duration of jaundice may be protracted, and the serum bilirubin may be elevated 3 months.[118]

The laboratory findings are characteri by a maximum serum bilirubin of from to 29 mg. per cent, negative cephalin flocc lation and thymol turbidity tests, moder elevation of the serum alkaline phosphat and a reduced serum cholesterol ester fr tion.[118] The serum albumin and globulin terminations are normal. In the early sta of the disorder the urine contains bile, a the stools may be clay-colored. There m be prolonged absence of urobilinogen in urine.[10]

The histologic lesion as revealed in nee specimens is that of stasis of the bile w plugging of the bile canaliculi in the cent zones of the liver lobules and a very m hepatic cell damage in these areas. There no evidence of obstruction of the biliary s tem distal to the central zones. While exact mechanism of the jaundice is not cle Werner and associates have suggested t injury to the hepatic cells by the drug le to a disturbance of the normal hydration the bile which becomes too viscous to fl through the intralobular duct system.

It is important to bear this entity in mi since it may be mistaken for extrahep obstructive jaundice and lead to unnecess laparotomy.

CHRONIC IDIOPATHIC JAUNDICE WIT UNIDENTIFIED PIGMENT IN THE LIVE

Recently, Dubin and Johnson have ca attention to a form of chronic idiopat jaundice that occurs in young adults. It perficially resembles constitutional hep dysfunction and also has been confused w obstructive jaundice and chronic viral he titis. According to these authors, the co monest symptoms are abdominal pain fatigue, jaundice, dark urine and slight largement of the liver. The jaundice fluc ates in intensity and is aggravated by in current diseases. The disease differs fr constitutional hepatic dysfunction in (1) the urine is dark, (2) the serum bil bin shows an increase in the 1-minute prompt-reacting bilirubin, (3) liver funct tests are often abnormal, and (4) the g bladder fails to visualize on roentgen exa nation. Needle biopsy of the liver rev

presence of a brown pigment in the he-
parenchymal cells in an otherwise nor-
organ. The pigment in the liver cells is
et unidentified, although it has certain
chemical properties in common with
ids and lipochrome pigments. Although
tiology of the disease is not known, the
ors are inclined to believe that it prob-
consists of an inborn deficiency of the
, characterized by multiple defects in
bolism whereby the liver cannot prop-
excrete such substances as bilirubin, the
ent that accumulates in liver cells,
nsulphalein and dyes used in cholecys-
aphy.

Infectious Mononucleosis

nfectious mononucleosis undoubtedly is
uently mistaken for infectious hepatitis.
reported incidence of jaundice in infec-
s mononucleosis has ranged from 0 to 13
cent.[1] In most cases the jaundice has
mild and of short duration, although in
e instances it has been observed to last
11 weeks[1] and to reach a high degree of
nsity.[1, 15, 36]

he atypical lymphocytes may resemble
ely those seen in infectious hepatitis, as
the physical findings of lymphadenop-
, a tender liver and splenomegaly, and
occurrence of positive flocculation tests.
erentiation may be made only by means
he heterophile agglutination test. In order
void error, it should be remembered that
test is frequently negative in the first
eeks of the disease[35] and may not be-
e positive until 8 weeks after onset.[1]
clinician should consider infectious
onucleosis in a patient with suspected
atitis when jaundice is mild and fever is
present, when the total white count is
ated and when the serum alkaline phos-
tase[32, 74] and the gamma globulin[102] are
eased. He should repeat the heterophile
lutination test when it is negative. Occa-
ally, positive heterophile tests may occur
iral hepatitis,[46, 63] but the antibodies are
to be absorbed by guinea pig kidney and
by beef red cells, the reverse of the
ern of absorption that occurs in infec-
s mononucleosis.

n some instances differentiation may be
le by liver biopsy which may show distention of the sinusoids with atypical lymphocytes. The differentiation of infectious mononucleosis and viral hepatitis is of practical importance, since it may do away with the necessity of observing enteric precautions and giving prophylactic inoculations of gamma globulin. Furthermore, it would appear safer theoretically to use the blood of a patient with infectious mononucleosis for donor purposes after a 2-year period. According to Havens,[45a] attempts to transmit infectious mononucleosis to volunteers have been quite unsuccessful, with the exception of a Scandinavian report. (See also p. 416, Chap. 13).

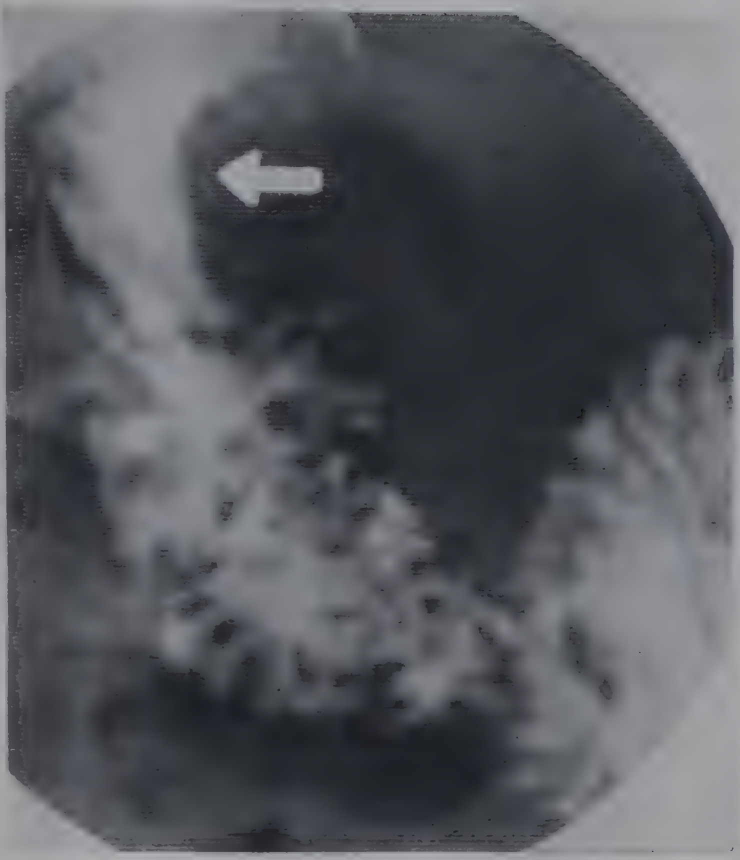

Fig. 67. A.T. 22038. Duodenal defect from multiple common duct stones.

Roentgen Changes Suggesting Periampullary Tumor

The author has seen at least 3 middle-aged patients with viral hepatitis wrongly diagnosed as having carcinoma of the ampulla of Vater, chiefly because of x-ray changes in the descending duodenum. Therefore, it is important to realize that such changes may occur in infectious hepatitis, as pointed out by Markoff. Presumably they are due to edema or inflammation in the periampullary region. It is conceivable that they may be caused by aberrant pancreatic tissue in some cases. Sometimes a duodenal defect simulating that produced by periampullary tumor may occur in cases of common duct stone (Fig. 67).

Cholangiolitic Hepatitis

A stumbling block to diagnosis and perhaps also to the classification of jaundice is a group of cases with what is probably (physiologic) intrahepatic obstruction and designated by Watson and Hoffbauer as cholangiolitic hepatitis.[113, 114] These cases present a clinical picture in keeping with hepatitis, but the laboratory tests are sugg tive of obstructive jaundice. In some i stances operation and operative cholangi grams have been required to exclude ext hepatic obstruction. My colleague, Edwa A. Gall, believes that they represent a va ant of viral hepatitis with changes hig lighting the ductular system and with e dences of obstruction.[33] These chang usually are accompanied by histologic alte tions characteristic of viral hepatitis. Simil histologic changes are found without labo tory evidence that is suggestive of obstru tion.

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apter 8

PORTAL HYPERTENSION

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INTRODUCTION

Portal hypertension develops as a result the increased resistance to the normal flow of blood from the portal bed into systemic venous system (1) because of intrahepatic block, due to the interlobu- scarring and the regeneration of liver ules secondary to portal cirrhosis, or (2) cause of an extrahepatic block due to an struction of the portal vein itself, usually result of venous thrombosis, or in a rare e congenital atresia. The pressure in the rtal vein is not extremely great in these nditions, since usually it is found between and 45 millimeters of mercury, or 30 to centimeters of water.[11] It is believed that addition to the portal hypertension there o exists portal hypervolemia, another im- rtant factor that plays a vital role in the thologic physiology of portal bed block. e general pathologic picture of portal bed ock usually develops over a period of years d may not be associated directly with the imary cause of the block. This is especially e in cases of cirrhosis of the liver. It is portant to remember from the therapeutic wpoint that the correction of the bleeding dency from esophageal varices by reduc- g the state of portal hypertension by some pe of venovenous anastomosis between the rtal and the systemic venous systems has le if any effect on improving the condition the diseased liver other than protecting it m the ravages of repeated blood loss from vere hemorrhage. Therefore, the treatment the cirrhotic liver should be entirely sep- ate and should be continued indefinitely in ost cases.

Sudden occlusion of the portal vein by interruption of it in a normal human being results in an extreme degree of portal hypertension, and death usually ensues within a few hours because of hemorrhagic shock resulting from the pooling of the great majority of the circulating blood in the splanchnic area. The portal vein is unique in this regard since practically any large venous channel in the body, except the inferior vena cava, proximal to the renal veins may be interrupted without serious consequences to the individual. This is due to the paucity and the small size of the collateral venous channels that allow blood to escape from the portal area into the systemic venous system. The obstruction that results from disease, on the other hand, is usually compatible with life at least for varying periods of time, since it is a gradual process in most instances, permitting the venous collateral channels to dilate and so allow the portal blood to bypass the site of obstruction. As a result the degree of hypertension is not as marked as in acute obstruction of the portal vein, and although it may be 3 or 4 times the normal portal venous pressure, the actual level is not extremely high; therefore, it is believed that too much emphasis has been placed on the term "hypertension" in these conditions, and not enough on the portal bed hypervolemia which it is believed is increased greatly.

As a result of the obstruction to the outflow of the portal venous blood, definite changes take place in the individual which are not compatible with good health. These include changes in the cellular constituents of the blood, due in part to a hyperactivity of the spleen—so-called congestive splenomegaly or hypersplenism.[22] Marked changes may occur also in the functions of the liver in the intrahepatic group and also late in the course of the disease in long-standing cases of the extrahepatic type of portal bed block. One of the most significant changes which occurs, however, is vascular in nature, especially since it represents a serious threat to an individual's life. Thus as a result of the partial obstruction to the outflow of blood from the portal bed with the resulting state of portal hypertension and hypervolemia, marked engorgement and enlargement of the venous collateral channels develop, especially of the submucosal veins of the lower portion of the esophagus. These are termed esophageal varices. Although ill health may result from the primary liver disease and the secondary blood changes, it is of extreme significance that death may occur with cataclysmic suddenness from rupture of these esophageal varices due to exsanguinating hemorrhage. This is much more likely to occur in patients with cirrhosis of the liver than in those with the extrahepatic type, since patients with normal livers can withstand severe bleeding better than those with diseased livers.

TYPES OF PORTAL BED BLOCK

The intrahepatic type of portal bed block is the most common form of the disease complex. It occurs most frequently in portal or Laennec's cirrhosis of the liver. The cause of the block to the flow of blood through the liver is the narrowing of the vascular pathways due to fibrosis in the interlobular spaces and the distortion of them by the islands of regenerating liver cells. It apparently is an irreversible process that is not amenable to surgical treatment except in so far as portacaval shunts will reduce the portal hypertension and prevent bleeding from the esophageal varices. The cirrhosis frequently seen in the chronic alcoholic patient usually is believed to be the most common type of this disease. The following analysis of a series of patients with portal cirrhosis, operated upon for bleeding esophageal varices at the Massachusetts General Hospital between 1945 and 1952, inclusive, reveals that other etiologic factors than alcohol were the cause of the cirrhosis in many cases. There were 68 patients in this group, in all of whom liver biopsies were obtained. It was found th there were only 18 (26%) who gave a h tory of alcoholism and were diagnosed as t alcoholic type of portal cirrhosis. T remainder of the group was made up nonalcoholic patients, and the patholo diagnoses in them were as follows: (34%) were an unclassified type of por cirrhosis; 15 (22%) were the postnecro type 4 (6%) were the postatrophy typ 4 (6%) had portal cirrhosis develop se ondary to biliary cirrhosis; 3 (4%) we the toxic type; and 1 (1%) showed por cirrhosis secondary to sarcoidosis. The clas fication of these various types is difficult fro the pathologic viewpoint, and there is mu to learn about the etiology of them. Howev it seems to be obvious from these statist that there is probably no single etiologic fa tor and that alcohol played a role only approximately one quarter of this group patients. Another type of portal cirrho seen commonly in the tropical countries, l observed only rarely in the temperate zo is that due to schistosomiasis. A portal b block of intrahepatic origin is encounter also in the rare condition of thrombosis the hepatic vein. It is a fatal disease if unr ognized and untreated by a portacaval shu

From the practical surgical aspect portal bed block a cavernomatous transf mation of the gastrohepatic ligament may encountered which makes the exposure the portal vein extremely difficult and haza ous, in some cases even impossible. Unf tunately, there is no means available determine the presence of this vascular normality prior to operation. It is observ more commonly in the extrahepatic type portal bed block and is one of the main r sons why a splenorenal shunt is preferred this type of disease. Fortunately, in the int hepatic portal bed block this cavernomato change is encountered only in a relatively f cases, so that in this group direct portaca shunts are done more frequently. The path genesis of cavernomatous transformation not definitely known. By some it is co sidered to be the result of portal vein thro bosis with recanalization; by others, to b congenital lesion; and by still others, neoplastic vascular lesion such as a hema gioma. As the result of observations fro ating on a number of these cases it seems the cavernomatous change is in the ohepatic ligament rather than in the porein itself, and that it represents one of re's methods of developing collateral nels between the portal bed and the , since it is seen most commonly in pas with an extrahepatic block due to an uction of the portal vein. As additional ence of this theory, it has been observed few cases of cirrhosis of the liver which ound to have a thrombosis of the portal a condition that apparently develops as esult of a marked degree of intrahepatic al bed block.

he extrahepatic type of portal bed block bserved less commonly than the intratic. In a group of 97 patients operated at the Massachusetts General Hospital bleeding esophageal varices during the ar period from 1945 to 1952, inclusive, 30%) of the patients had this type of k, while 68 (70%) had the intrahepatic . The pathogenesis of this disease process t completely understood, but there seem a congenital and also an acquired form. former type is relatively rare. The portal block in these cases is due to a congeniobliteration or atresia of the portal vein , which has been reported by others[26] ot seen in our cases. In a few other cases believed that the obliterative process h closes the umbilical vein may extend volve the portal vein, since they are in inuity at birth.

he great majority of the patients have acquired type of portal bed block, the lt of a thrombosis of the portal vein or main tributaries. This condition may r in the early postnatal period secondary omphalitis with an ascending thrombobitis in the umbilical vein, which vessel the left branch of the portal vein, and ugh this osculation the thrombotic procnay extend into the portal vein. Fortuly, with the advent of the antibiotics this ic type of thrombophlebitis arising from mphalitis is seen less frequently, so that r cases of bleeding esophageal varices in very young are being encountered today. al thrombosis, like venous thrombosis where in the body, may develop secondto trauma in a rare instance, or more commonly may appear spontaneously. This type of the disease has been seen to develop suddenly as late as the seventh decade.

The treatment of choice in all patients with the extrahepatic type of portal bed block is a splenectomy and the construction at the same operation of an end-to-side splenorenal shunt. Failure to do the latter at this time may preclude forever the establishment of a portacaval shunt because, as noted above, a cavernomatous change exists in the gastrohepatic ligament in the majority of the extrahepatic group of patients which may prevent isolation of this vessel; in addition in most of these cases, when the portal vein has been exposed it is unsatisfactory for the construction of a shunt because the lumen of it has been destroyed by the thrombotic or obliterative process that originally involved it.

A combined type of intrahepatic and extrahepatic block has been observed in 4 of our cases, an incidence of approximately 4 per cent. The primary condition in all these cases has been a portal cirrhosis, apparently with a marked degree of intrahepatic block resulting in a slowing of the blood flow through the portal vein, so that a spontaneous venous thrombosis had developed in this vessel (Fig. 68). A satisfactory direct portacaval shunt has been established in 3 of these 4 patients by first performing a thrombectomy of the portal vein (Table 9).

TABLE 9. TYPES OF PORTAL BED BLOCK

1. INTRAHEPATIC*
   - A. Portal cirrhosis (Laennec type)
   - B. Cirrhosis secondary to schistosomiasis
   - C. Thrombosis of hepatic veins
2. EXTRAHEPATIC
   - A. Congenital obliteration of the portal vein
   - B. Thrombosis of the portal vein
     - a. Infectious
     - b. Idiopathic
     - c. Traumatic
3. COMBINED INTRAHEPATIC AND EXTRAHEPATIC PORTAL CIRRHOSIS WITH SECONDARY PORTAL VEIN THROMBOSIS

* This type may have a cavernomatous change in the gastrohepatic ligament but more commonly does not, whereas in the extrahepatic type this vascular change is found to be present in the majority of cases.

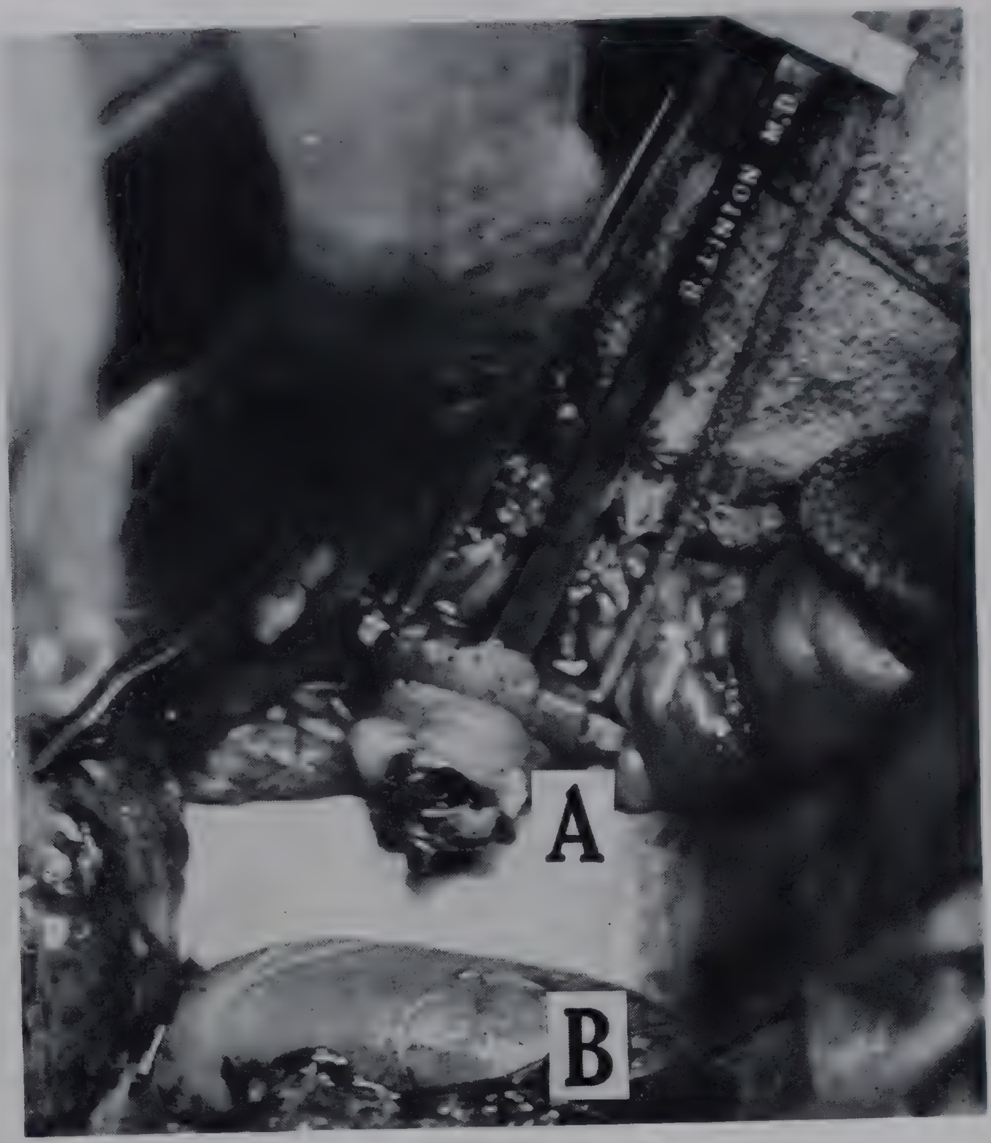


FIG. 68. A photogr
taken at the time of constr
ing a direct end-to-side an
tomosis between the po
vein A and the inferior v
cava B. Note the throm
protruding from the di
end of the severed po
vein. This patient, a man a
46 years, had typical po
cirrhosis with bleeding
phageal varices. A satis
tory shunt was constru
after removing the throm
from the portal vein.

VASCULAR ANATOMY OF THE PORTAL BED

The portal venous system is unique for a number of reasons. First, it consists of 2 capillary beds: one in the gastro-intestinal organs, the pancreas and the spleen, and the other in the liver. They are connected by the portal vein and its tributaries which collect the blood from the former and then deliver it to the latter. Second, the venous pressure in the portal vein and its tributaries is higher than in the systemic veins in this region of the body because the blood must be forced through the second capillary bed—the liver sinusoids. The normal portal pressure has been reported to range between 14 and 22 cm. of saline, according to Bellis,[3] and between 6 and 14 cm., according to Whipple,[46] whereas the normal systemic venous pressure is approximately zero. Third, the collateral venous channels between the portal and the systemic venous systems are relatively small in size and few in number, so that sudden occlusion of the portal vein itself results in
death from the reduction in the circula
blood volume due to the trapping of la
quantities of blood in the splanchnic a
This is not true of the large systemic ve
since even the inferior vena cava may
interrupted without serious effects if i
performed distal to the renal veins. Fou
unlike most other veins in the body th
blood vessels contain no valves, so that
direction of blood flow in them may be
versed. This is a fact of extreme significa
in the consideration of venous shunt surg
because it makes it possible to bypass ei
an intrahepatic or an extrahepatic type
portal bed block.

The arterial blood enters the splanc
bed through (1) the celiac axis and
branches, the left gastric, the splenic
the hepatic arteries, (2) the superior me
teric artery and (3) the inferior mesent
artery. The blood is distributed from ther
the gastro-intestinal tract, the pancreas,
spleen and the liver. It is collected from th
structures and organs by the coronary
of the stomach, the splenic vein and the

r and the inferior mesenteric veins. The or mesenteric vein unites with the ic vein, and the latter with the superior nteric vein to form the portal vein. The nary vein sometimes arises from the ic vein, but most frequently it joins tly with the portal vein.

e blood flow to and through the liver interest, since this organ is supplied by arterial and venous blood, the former e hepatic artery, which is said to furnish oximately 25 per cent of the blood ly to it in the normal individual. As first ed out by Gad, the hepatic arterial flow wo functions: (1) to supply oxygen to iver cells and (2) to control in part the us blood flow through the liver. The is accomplished in part due to the fact the liver is a spongelike structure. As sult of the high arterial pressure, the n develops a certain degree of turgidity h exerts a variable degree of pressure e liver sinusoids, depending on the arte- blood pressure level, and, therefore, ance to the flow of blood through them. w arterial pressures the portal bed will y more readily than at higher levels of mic arterial pressure.

e remaining 75 per cent of blood flow- hrough the liver is supplied by the portal This blood is relatively hypoxic so that iver does not depend on it for oxygen. chief function, on the other hand, is to nutrient material from the intestines torage in the liver, and insulin from the reas, and to carry away from it materials as glycogen that have been stored in iver cells. In addition, and of extreme rtance, toxic materials resulting from reakdown of proteins in the intestinal which are absorbed by the blood stream arried through the liver where they are xified before the blood passes on into general circulation. When all the portal d is made to bypass the liver by means n anastomosis between the portal vein the inferior vena cava, the detoxifying tion of the liver may be impaired seri- with dire consequences, especially in nts with normal livers. Fortunately, the effects of portacaval shunts are not so ed in many of the patients with portal rtension due to an abnormal increase in the arterial blood flow through the hepatic artery seen in this condition. This is thought to be explained by the fact that the blood, although it does not go directly from the intestinal tract to the liver, does reach it in greater quantity per unit of time because of this increased arterial blood flow through it, especially in the cirrhotic liver. Another factor may be that the body has adjusted itself to the effects of the toxic substances as a result of the existing natural vascular shunts which, because they are small, are not effective in reducing the state of portal hypertension but permit a considerable amount of blood with its toxic materials to bypass the liver, so that the body may develop a certain degree of immunity to them.

The natural collateral pathways, according to Pick's[31] classification, are made up of two sets of blood vessels: "the hepatopetale" and "the hepatofugale." The former shunt the portal blood to a very limited extent into the liver in the extrahepatic type of block when the blood flow through the liver is unobstructed. The vessels consist of the veins of Sappey or accessory portal veins which originate in some organ other than the digestive tract and pass through the liver capsule to ramify in its substance, which include the so-called deep cystic veins; the veins in the gastrohepatic omentum; the hepatocolic and the hepatorenal veins; the veins of the suspensory ligament and the diaphragmatic veins.

The hepatofugale vessels constitute the most important natural channels that shunt the portal blood into the systemic venous system in both the intrahepatic and the extrahepatic types of block, but, even so, the total amount of blood is relatively small. These vessels are found between the gastrointestinal tract and other organs of the abdominal cavity where they lie retroperitoneal or attached to the parietal peritoneum. The largest and most numerous of them are seen frequently in the diaphragmatic, peritoneal and retroperitoneal attachment of the spleen. They are known as the veins of Retzius. In a few cases direct connections between the veins of the splenic pedicle and the adrenal vein which drain into the renal vein have been observed while performing splenorenal shunts.

Because these collateral channels are necessarily severed in performing a splenectomy, the performance of this operative procedure without the construction of an end-to-side splenorenal shunt in a patient with bleeding esophageal varices will throw an additional load on these latter vessels with a resulting increase in the state of portal venous hypertension and, in many instances, an increased incidence of esophageal hemorrhage from the distended esophageal varices.

Other hepatofugale vessels are found at the site of the obliterated fetal circulation, the para-umbilical veins in the round ligament of the liver. They join the veins of the anterior abdominal wall and sometimes appear in a swollen state to radiate out under the skin around the navel; they are termed a "caput medusa." Two other groups of these veins are found at the junction of the two ends of the gastro-intestinal tract. The ones at the lower end, or anus, join the portal and systemic systems through the hemorrhoidal veins. The vessels at the other end of the gastro-intestinal tract at the cardio-esophageal junction perhaps are the most important of all the collateral channels that shunt the portal blood, but it is extremely doubtful if they are effective bypass pathways, because it is the enlargement of them with their subsequent rupture that is the cause of the high morbidity and mortality rates in patients with portal hypertension. They have been thought to constitute a channel of egress between the portal system and the azygos system through the veins of the cardia of the stomach, but it seems more likely that they are simply blind ends of the large dilated venous channels in the reservoir of the portal bed, because only in very few instances does one find enlarged periesophageal veins connecting the esophagus with the intercostal veins and the azygos system. Furthermore, the amount of portal blood shunted into the systemic venous system by the esophageal varices is not commensurate with the enormous size of them. When rupture of these vessels occurs it is as if a sluice gate in a dam were opened suddenly, because of the massiveness of the hemorrhage. Frequently, the blood is vomited in large amounts when the hemorrhage is massive; when less, it is passed only by rectum.

PATHOLOGIC PHYSIOLOGY OF PORTAL HYPERTENSION

As pointed out above, there is an int
relationship between the portal venous a
arterial blood flow through the normal liv
According to Elias[32] and Kelty,[21] the arter
capillaries may join the sinusoids in the pa
the portal, or the intralobular regions, a
the blood from them is drained out throu
the efferent central collecting veins.
shown by Herrick,[17] in 1907 and confirm
by others, in the normal liver there is o
a slight regurgitation of the hepatic arter
blood into the hepatic portal venous radica
because there is no abnormal mechani
obstruction to the flow of blood from t
liver sinusoids. In portal cirrhosis of t
liver, changes take place in this hemodynan
arrangement which, it is believed, play
role in the state of portal hypertension. H
rick[17] has shown by perfusion experime
of the liver that at an arterial blood press
of 130 mm. of mercury in the normal li
some blood flows into the portal vein, a
a pressure of 13 to 14 mm. of merc
develops in it, whereas under similar per
sion experiments of livers with portal cirr
sis, the portal pressure rises several ti
higher to 30 to 40 mm. of mercury. Th
experiments and others he performed dem
strated that there is a marked regurgitat
of arterial blood into the intrahepatic po
venous radicals in portal cirrhosis and t
there is a much freer communication in
condition between the arterial and the ven
channels than in the normal liver.

It is believed that this abnormal capill
type of arteriovenous shunt within the li
in portal cirrhosis is an important factor
producing the state of portal hypertens
and hypervolemia. Additional factors are
the larger volume flow through the hep
artery observed in the cirrhotic liver as c
pared with the normal and (2) the obstr
tion to the venous outflow through the
patic veins, the result of fibrosis and
irregular masses of regenerating liver c
These abnormal pressure relationships,
believed, give the only rational reason for
interruption of the hepatic artery as a met
of treatment of portal hypertension. It sho
be noted, however, that since this surg

cedure is so unphysiologic from other dpoints, and since so many patients dep liver necrosis from interruption of the atic artery, this method of treatment is to condemned.

Contrary to Banti's[1] original conception, doubtful that there is any primary paogy in the spleen to explain the various nges in the blood and in the organs of splanchnic area which occur in patients portal bed block. Instead, the pathologic nges of the spleen (including splenoaly, fibrosis of the capsule, and the microbic changes in the splenic pulp described Whipple[46]), the abnormalities of the cellu- constituents of the blood, and the vascu- changes in the esophagogastro-intestinal t, including the dilatation of the submual esophageal veins to a varicose state believed to develop secondary to the e of portal venous hypertension and hyvolemia. Some of these changes, even ugh the portal venous pressure may be uced to a normal level by a portacaval stomosis, do not revert to normal; thus enlargement of the spleen, especially in g-standing cases, does not reduce to its mal size, undoubtedly the result of fibro- of this organ, nor do the esophageal ices always disappear. On the other hand, secondary blood changes often revert to mal, especially in those patients with entially normal livers. In a relatively young ient, with an extrahepatic type of portal l block, or in one who has developed it ently, there is surprisingly little morphoic or functional change in the liver despite impairment of the portal venous supply t. Undoubtedly, in long-standing diseases his type of portal bed block, liver changes h as cirrhosis may develop eventually, but s believed they are probably secondary to same primary etiologic factors that proe this disease.

The normal portal venous pressure under ic conditions has been difficult to ascer- in the human because it has rarely been ermined except during the administration an anesthetic while performing a surgical arotomy. Factors such as the depth and type of anesthesia, and the level of the tolic blood pressure influence the actual el to a considerable degree. From observations that have been made, however, it is probably safe to say that the normal venous pressure after opening the abdomen during a surgical operation varies between 6 and 20 cm. of saline, so that pressures above the latter figure indicate the presence of a portal bed block with portal hypertension. Portal pressures in patients with bleeding esophageal varices secondary to intrahepatic and extrahepatic portal bed block have frequently been found to be 4 to 5 times the normal level.[11] In our clinic the highest level encountered has been 54 cm. of saline. The majority lie between 40 and 50 cm. So far as the blood pressure within the veins of the portal bed is concerned, it is relatively low when compared with that in the veins of the lower extremity while in the standing erect position, and yet rupture of the latter with hemorrhage is a relatively rare condition. The course of events that leads to fatal exsanguination from bleeding esophageal varices would indicate that their rupture results perhaps from trauma or peptic digestion of the esophageal mucosa over them, rather than the increased pressure within them. The relief of bleeding from the esophageal varices following shunt surgery would indicate that it is not so much the reduction in venous pressure in the portal area as it is the shunting of a large volume of dammed-up blood in the portal area, since the venous pressure after completion of the shunt still may be above the normal range, but bleeding from the esophageal varices rarely occurs.

DIAGNOSIS OF PORTAL HYPERTENSION

The diagnosis of portal hypertension, as a rule, is not difficult, especially if it is possible to demonstrate esophageal varices, because their presence almost without exception indicates that there is an obstruction to the normal outflow of the portal venous blood with a resulting elevation of the portal venous pressure—a state of portal hypertension. As pointed out by Whipple,[46] there is a definite clinical syndrome that is seen in portal bed block with portal hypertension characterized by a variable secondary anemia, a leukopenia, a thrombocytopenia, splenomegaly, and repeated esophagogastrointestinal hemorrhages; furthermore, the liver may or may not be cirrhotic, depending on the site of the portal bed block. This syndrome was first recognized and reported by Banti[1] in 1883. It was his opinion that some unknown toxic agent, elaborated in t spleen, resulted in splenomegaly and lat cirrhosis of the liver. However, addition studies by others have revealed that the l sions in the fibrillar reticulum which he co sidered pathognomonic of the condition we

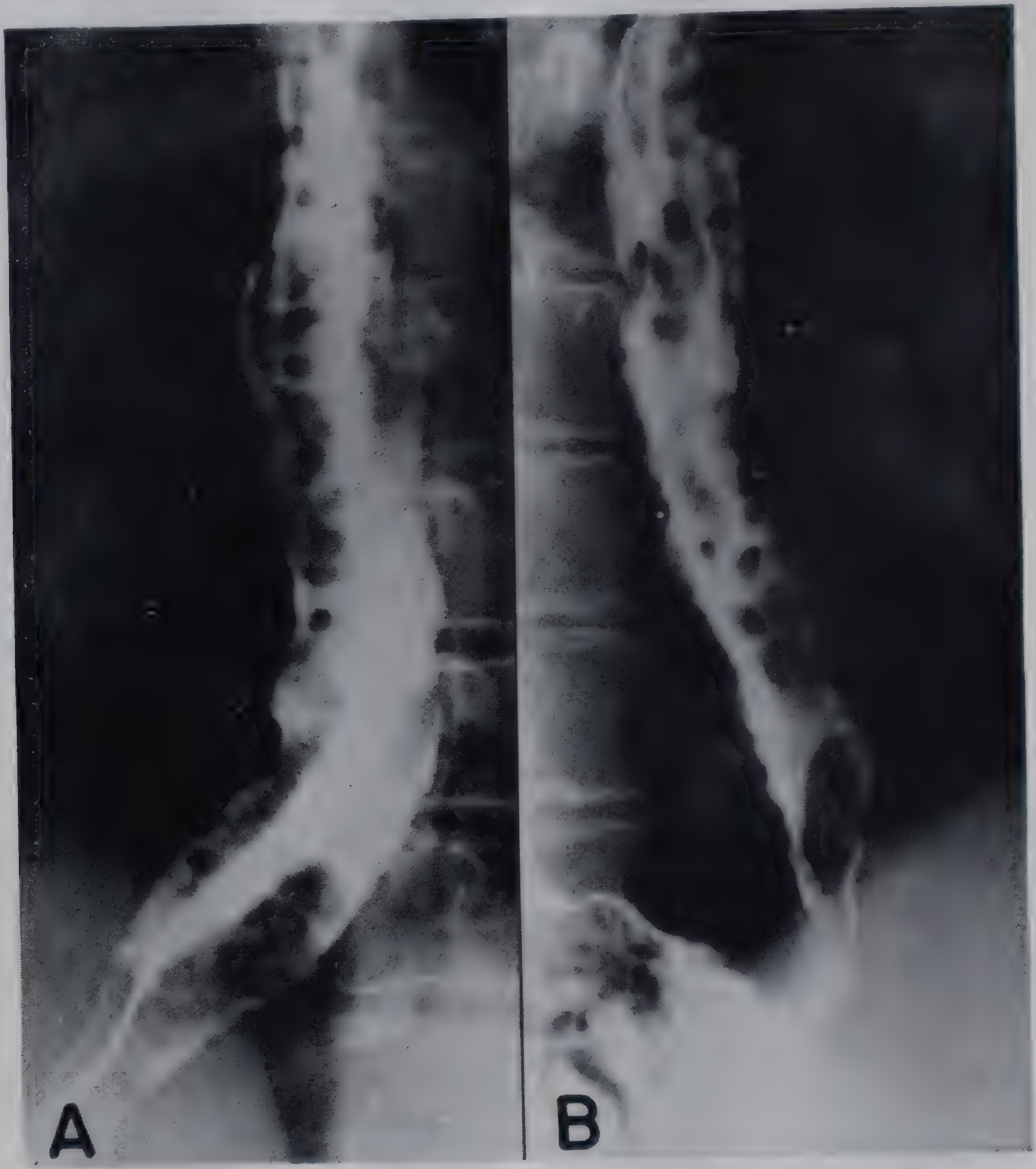


Fig. 69. Photographic reproductions of roentgenograms of the esophagus, demonstrating huge esophageal varices, extending from the upper thoracic level throughout the entire lower esophagus in a patient with intrahepatic portal bed block secondary to portal cirrhosis. The demonstration of these blood vessels in this manner is proof that a portal bed block with portal hypertension exists. Note the marked widening of the lower end of the esophagus, a common finding in patients with esophageal varices. The esophageal varices appear as the dark irregularly shaped masses outlined by the barium sulfate mixture. (A) The exposure of this roentgenogram was a left anterior oblique view. (B) This view was taken in the right anterior oblique manner to separate the esophageal outline from that of the bodies of the vertebrae. These two roentgenograms were on the same patient. The two views are obtained in order to outline the esophagus in different perspectives to demonstrate varices which may not show in one, but may in the other. This patient underwent a successful splenorenal shunt with considerable reduction in the varices but not complete disappearance of them.

lom found in the majority of cases. In v of our present knowledge it is generally eed that it is doubtful if there is a disease ty that can be termed "Banti's disease"; efore, it would seem best to abandon term.

he occurrence of gross esophagogastro-stinal bleeding is frequently the symptom compels the patient to seek medical ntion. However, the disease undoubtedly present in many cases for a matter of rs before this serious complication mani-s itself. Certainly, any patient with spleno-galy, either with or without gastro-intesti- bleeding, should be suspected of having tal hypertension. The differential diagno-in those cases without bleeding must rest accurate hematologic studies and care- roentgenographic examination[37] of the phagus, or the direct examination of this cture by esophagoscopy for varices. If y are found to be present, it adds sub-ntially to the diagnosis of a portal bed ck and, in fact, can almost be considered hognomonic of it (Fig. 69). However, ure to disclose them does not rule out the gnosis, since they are notoriously difficult demonstrate. In some clinics the esopha-copist is called upon to determine their sence or absence, but in the majority of es a roentgenologist well trained in this d will be able to visualize the vast ma-ity of them and with less risk of causing m to bleed.

Liver function tests are relied upon to ermine the site of the portal bed block her than to make a diagnosis of it (Table). Many liver function tests are available, the ones that have been found to be of st value are the bromsulphalein retention t, the serum albumin and globulin levels, cephalin flocculation test and the pro-ombin time. If there is a high retention of omsulphalein in the blood 45 minutes after intravenous injection of 5 milligrams per ogram, if there is a reduced level of serum umin, an elevated cephalin flocculation, to - or 4+, and an elevated prothrombin e, the diagnosis of an intrahepatic portal d block secondary to portal cirrhosis can made with assurance. Even if only one or o of the tests are abnormal, this diagnosis can almost be made with a certainty. When the values of these tests are all normal, the site of the portal bed block is extrahepatic and lies within the portal venous system. This latter type is much less common than the intrahepatic form but because of an essentially normal liver, the risk of performing surgery on these patients is much less than in the cirrhotic group. If additional evidence is needed to determine the state of the liver, a needle biopsy may be performed. This is not necessary as a routine procedure, but in some cases it gives valuable information to determine the operability of a given case.

TABLE 10. COMPARATIVE STUDY OF LABORATORY DATA IN TWO PATIENTS: ONE WITH EXTRAHEPATIC AND THE OTHER WITH INTRAHEPATIC PORTAL BED BLOCK

	INTRA-HEPATIC	EXTRA-HEPATIC
BLOOD PICTURE		
Hemoglobin	8.5	8.2
Red blood cells	2,500,000	3,000,000
White blood cells	2,000	7,800
LIVER FUNCTION TESTS		
Total protein	6.1	6.8
Serum albumin	2.5	4.2
Serum globulin	3.6	2.6
Prothrombin time	40%	80%
Cephalin flocculation	4+	negative
Bromsulphalein retention	50%	7%
Serum bilirubin	4 mg.	1.6 mg.

Visualization of the portal venous system by splenoportography is recommended by some.[35] This is accomplished by injecting 30 cc. of a 35 per cent solution of Diodrast into the splenic pulp, followed immediately by taking a roentgenogram of the abdomen. By this method it may be possible to localize the site of the block in the portal venous system and also the state of the portal and the splenic veins to determine whether a direct portacaval or a splenorenal shunt will be the more satisfactory to perform. In our clinic this method has not been utilized, because it carries some risk from splenic hemorrhage, and it has been our observation that if the spleen is definitely enlarged, the splenic vein as a rule will be enlarged correspondingly so that a satisfactory splenorenal shunt can be constructed. In some patients with cirrhosis of the liver in addition to an intrahepatic portal bed block, there is found an extrahepatic block due to thrombosis of the portal vein in which it has been possible to remove the thrombus and construct a satisfactory direct portacaval shunt. Under these conditions splenoportography would be misleading, indicating that such a shunt could not be performed. Another criticism of this phlebographic procedure is that the Diodrast solution is an irritating substance which may result in further thrombosis of the portal venous system, thereby jeopardizing the patency and the function of a constructed shunt.

TREATMENT OF PORTAL HYPERTENSION

Emergency Treatment of Bleeding Esophageal Varices

Any treatise on the therapy of bleeding esophageal varices is incomplete without considering the emergency treatment of this serious threat to a patient's life. The following statistical analysis is given to emphasize the grave nature of this condition in a group of 93 patients with bleeding esophageal varices who were admitted to the Massachusetts General Hospital during the 5-year period from 1946 to 1950 inclusive. It demonstrated clearly the importance of developing a method of treatment to control the bleeding from the esophageal varices at the time of acute hemorrhage. In this group of patients, 65 (70%) had an intrahepatic block and 28 (30%) had an extrahepatic block. Despite several esophageal hemorrhages in many of the latter group, there were no deaths, and it was possible in 23 (82%) of them to perform some type of portacaval shunt. These low mortality and high operability rates undoubtedly are the result of dealing with relatively young patients with essentially normal livers. The results in the patients with cirrhosis, on the other hand, leave much to be desired, since it was possible to perform shunts only in 33 (51%) of them because 32 (49%) died while in this hospital, either directly or indirectly from hemorrhage from the esophageal varices before shunt surgery could be performe
Exsanguination was the cause of death in
(72%) of these patients. Massive bleedi
in 4 (13%) of the others was a major fa
tor in causing liver failure from which the
patients died. The other 5 (15%) had mi
or slight hemorrhages which were a co
tributing factor in their deaths, also fro
liver failure (Table 11).

Table 11. Causes of Death in 32 Patien
with Bleeding Esophageal Varices
without Portacaval Shunt
Surgery
Massachusetts General Hospital, 1946 to
1950, Inclusive

Causes of Death	Extra-hepatic	Intra-hepati
Hemorrhage alone	0	23 (72%
Hemorrhage with secondary liver failure	0	4 (13%
Liver failure with slight hemorrhage	0	5 (15%
Total	0	32

Differential Diagnosis. The early diagnos
of the site of bleeding in a patient who su
denly develops a massive upper esophag
gastro-intestinal hemorrhage is of extren
importance in the proper management. T
usual measures to combat shock are carri
out first, including blood grouping and ear
transfusion. Since frequently blood pours o
of these patients as fast or faster than it c
be replaced by transfusion, it is of extren
importance to determine the origin of t
hemorrhage and, if possible, to differentia
bleeding from esophageal varices from th
of an ulceration of the stomach or duodenu
because the treatment of the two types
cases is very different. A careful physic
examination is of some help in making t
diagnosis of esophageal varices. The findi
of spider angiomata on the skin, a splen
megaly and an enlarged liver are suggesti
evidence of cirrhosis of the liver and th
the bleeding source may be esophage
varices, but since patients with cirrhosis m
bleed from gastritis, a gastric ulcer or
duodenal ulcer, a more nearly accurate dia
nosis of the source of hemorrhage is nece

y. One of the methods of making this
ferential diagnosis is to do an esophago-
am, using a small amount of barium. In
any patients in our clinic this has been a
ry useful procedure, but it requires a roent-
nologist who is well trained in the x-ray
amination of the esophagus. Another
ergency method used in some of the larger
nics, with a well-trained esophagoscopist,
the direct visualization of the esophagus
esophagoscopy. Many hospitals, unfortu-
tely, do not have a well-trained roent-
nologist or an esophagoscopist, so that
me other method may have to be resorted

Cardio-esophageal tamponade by means
an intragastric balloon which is passed
o the stomach attached to a two-lumen
be is a useful method to differentiate the
urce of upper gastro-intestinal hemorrhage,
addition to controlling it, if the source is
phageal varices. One lumen of the tube
used for aspiration of the stomach, and
e other to inflate the balloon after it has
en placed in the stomach. From 500 to
0 cc. of air is used to inflate the balloon;
en with about 2 pounds traction on the
ter end of the tube, the balloon is impinged
ainst the cardio-esophageal junction. By
s means bleeding from esophageal varices
n be controlled almost immediately, since
e blood escaping from them comes from
e large submucosal plexus of the veins in
e cardia of the stomach. If, on the other
nd, the bleeding continues, it is probably
ming from a gastric or a duodenal lesion.

Emergency Nonsurgical Treatment. Many
tients with bleeding esophageal varices may
handled by conservative measures which
nsist mainly of putting the esophagus and
e stomach at rest and feeding them by
renteral means with intravenous infusions
glucose, electrolytes and proteins, and re-
oring the blood volume with multiple blood
nsfusions. The amount of bleeding that
e patient has had and the rate at which
continues after the first few hours of admis-
on to the hospital usually will tell one
hether or not more drastic measures are
cessary. If the pulse and the blood pressure
not stabilize, and if vomiting of blood
ntinues, it is recommended that cardio-
phageal tamponade[36] with the intragastric
lloon be utilized. Sengstaken and Blakemore[38] have recommended a triple lumen tube with two balloons—one intragastric and the other intra-esophageal—both of which are inflated. They state that this method of control may be maintained for a number of days, during which time nourishment may be administered through the third lumen of the tube. A two-lumen tube with the intragastric balloon has been found to be as effective when traction is exerted on this tube to impinge the balloon at the cardio-esophageal junction. This method, unfortunately, has its drawbacks, because ulcerations of the esophagus may develop due to pressure from the balloons and the tube, from which some patients have succumbed. In addition, when the tube and the balloon are removed, recurring bleeding not infrequently develops, necessitating the reinsertion of the balloon. For this reason, it is important to have a more definitive method of controlling the hemorrhage in the serious bleeder, but it is to be emphasized that this method of tamponade is a very important procedure to obtain control of the bleeding while preparing to operate on the patient to suture the varices.

Crafoord[9] and Moersch[29] have recommended the injection of the varices with a sclerosing solution. This method has not proved to be satisfactory, because the bleeding source lies at the very lower end of the esophagus, and during the hemorrhage it is practically impossible to visualize this area in order to inject the varix that is bleeding.

Emergency Surgical Treatment. A number of surgical procedures have been recommended as emergency measures to control the massive bleeding that so frequently is the cause of death in these patients, but unfortunately the majority are ineffectual or carry too high an operative risk to warrant their use. These include:

Interruption of the Splenic Artery. This method was first advocated by Blain[5] and more recently by others,[14] but in our hands it has been of little or no value in the patient with massive bleeding, although it may control the slow ooze from the varices in an occasional patient. The purpose of the procedure is to reduce the portal hypervolemia by the amount of blood that the splenic artery carries. It was carried out in 8 patients in our clinic, but recurrent bleeding occurred in 6 (75%) of them, and 3 of the 8 patients (38%) succumbed to massive hemorrhage from the esophageal varices.

Interruption of the Hepatic and the Splenic Arteries. This procedure has been advocated by Rienhoff[34] and Berman[4] with the purpose of reducing the portal hypertension and hypervolemia, but it has proved to be of no value in the control of the bleeding state; in addition, the mortality rate from liver necrosis has been so high that the procedure should be abandoned.

Transection of the Cardia of the Stomach. A transabdominal transection and resuture of the cardia of the stomach, with ligation of the left gastric artery, has been recommended by Tanner.[43] This procedure has merit, since it interrupts the flow of portal venous blood from the large submucosal gastric veins of the stomach which feed the esophageal varices. It has the drawback, however, that it is a major abdominal surgical procedure which must be performed when the patient is in a poor condition. Furthermore, it invades the abdominal cavity, which may result in numerous vascular adhesions that will interfere with the construction of a splenorenal shunt at a later date.

Transthoracic Transesophageal Suture of Bleeding Esophageal Varices. It is believed the method of transthoracic transesophageal suture of the esophageal varices that has been used in our clinic[24] during the past 3 years is the most effective emergency procedure yet to be developed for the control of massive hemorrhage from esophageal varices. The following case report demonstrates the ineffectiveness of the commonly accepted methods of treating a severe case of bleeding esophageal varices secondary to cirrhosis of the liver, and that some other method of controlling these bleeding vessels must be developed in order to save patients' lives and allow time to prepare them for some type of portacaval shunt.

Case L.B. No. 695843. A white man, aged 47, was admitted to the Massachusetts General Hospital on March 24, 1950, with a complaint of vomiting of blood intermittently for a period of 3 weeks. He gave a history of chronic alcoholism of 30 years' duration. He was treated for a questionable bleeding duodenal ulcer at another hospital 21 months before this admission; bleeding probably arose from esophage varices at that time. Six months and 3 month previously he had had repeated attacks c bleeding, and 3 weeks before admission h was admitted to another hospital because o further episodes of hematemesis. He was treate in that hospital by means of balloon tamponad for approximately a week with cessation of th bleeding. Eight days after removal of the tube bleeding recurred. While he was in this othe hospital he received a total of 24 blood transfusions.

Physical examination revealed a pale, sallo complexioned, well-developed and nourishe man, but appearing to be very ill. The genera physical examination was essentially negative except for spider angiomata of the skin an enlarged liver and spleen. The blood pressur was 110 systolic and 60 diastolic.

Laboratory Examination. The urine was negative for sugar and albumin; the hemoglobi was 7.5 Gm.; white blood count, 14,500; va den Bergh test 2.4 mgm. per cent; prothrombi time 65 per cent of normal; total protein 4.6 Gm.; albumin 2.88 Gm.; globulin 1.81 Gm nonprotein nitrogen 45 mgm. per cent.

Because of continued bleeding the splen and the left gastric arteries were ligated an divided under ether anesthesia 3 days after h admission on March 27, 1950. Following th operation the patient stopped bleeding for few days, and his hemoglobin rose to 13.6 Gr with daily transfusions, but on April 5, 1950, days after the operation, his stools becan grossly bloody again, and the following da his hemoglobin had dropped to 11.6 Gr There had been definite improvement in h serum protein by this time with a total prote of 6.73 Gm., albumin 3.7 Gm. and globul 3.03 Gm., and the nonprotein nitrogen h dropped to 29 mgm. per cent. On April 10, 195 his hemoglobin dropped to 9.5 Gm., indicati further bleeding. On April 17, 1950, despi continued daily transfusions, the hemoglob continued to drop to 8.8 Gm. At this time vomited considerable black blood, so cardi esophageal tamponade with an intragast balloon was reinstituted. On April 18, 195 the bleeding was controlled, so the balloon w removed, but it had to be reinserted 2 da later because of recurrent bleeding, which w only partially controlled. On April 21, 19 the patient died of a combination of hem rhage and liver failure.

Postmortem examination revealed portal c rhosis of the liver and esophageal varices wi massive gastro-intestinal hemorrhage. T urce of bleeding was found to be a small ening about 2 mm. in diameter in one of esophageal varices about 5 cm. above the rdio-esophageal junction (Fig. 70).

Comment. This man, aged 47 years, demonstrates the ineffectiveness of controlling esophageal bleeding in some patients with cirrhosis of the liver by generally accepted measures.

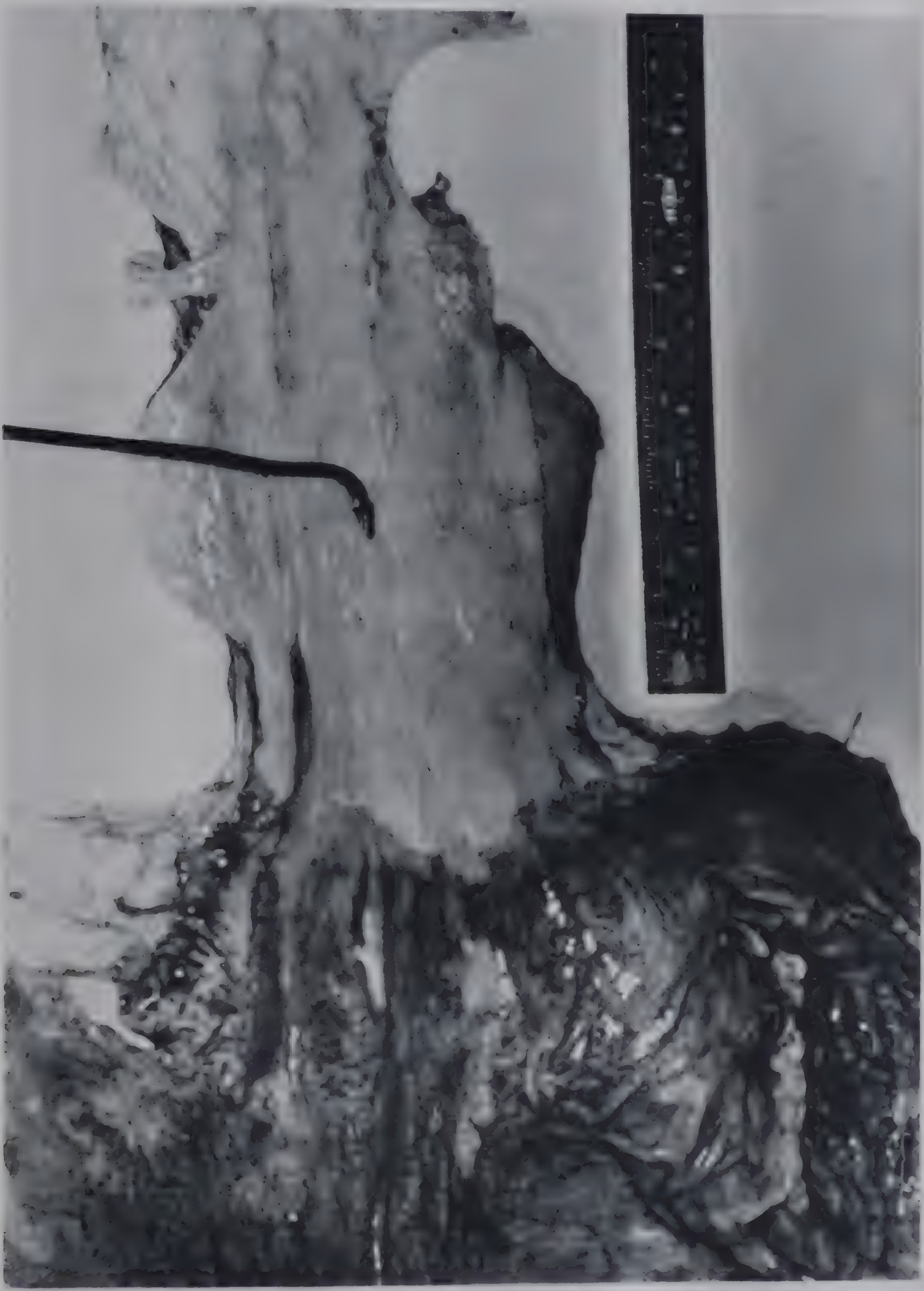


FIG. 70. An autopsy specimen of the opened distal end of the esophagus and the cardia of the stomach from a patient who succumbed to repeated massive hemorrhages from a ruptured esophageal varix and liver failure, despite the use of cardio-esophageal tamponade with a balloon tube and also the interruption of the splenic and left gastric arteries (see Case Report). The tip of the probe lies in a 2-mm. opening of the ruptured varix, through which the patient exsanguinated. There was a direct communication between it and a large submucosal vein of the stomach. This case first suggested the feasibility of exposing the bleeding esophageal varix to control it by suture in order to save the lives of many of these patients that were dying from exsanguination. (Linton, R. R., and Warren, R.: Surgery 33:243-255)

Despite interruption of the splenic and the left gastric arteries, the repeated use of cardio-esophageal tamponade and repeated blood transfusions which in this case totaled 55 in the last 52 days of his life, totaling 27,500 cc. of blood, this patient continued to bleed and died from esophageal hemorrhage and liver failure. The finding at autopsy of a small opening in an esophageal varix no larger than the diameter of a match was of extreme importance, since it was through this small opening that this man's life blood escaped. Therefore, at that time it was decided that in future cases of a similar nature, a direct attack should be made on the bleeding varix at the time of acute hemorrhage to control it by suture or by ligation, since by this method not only could a life be saved but also vast quantities of blood transfusions could be conserved for other patients.

These observations demonstrate clearly that an early, effective and safe means of controlling the ruptured esophageal varix at the time of acute hemorrhage is necessary in many patients to prevent death from uncontrollable bleeding and liver failure so that they may have the benefit of shunt surgery.

The control of serious hemorrhage, whethe it arises from a large artery or a vein, i obtained best by a direct exposure of th blood vessel with control of it by ligature c suture. In view of the advances made in re cent years in (1) surgical technic that pe mits an open thorax during a surgical proce dure, (2) anesthesia, (3) the availability c large quantities of blood by the establish ment of blood banks and (4) the availabilit of the antibiotics, it is now possible to ex pose the more remote regions of the bod where bleeding vessels occur that endang the life of the patient, such as a bleedin esophageal varix. It is recommended, there fore, that the transthoracic transesophage exposure of the esophageal varices at th distal end of the esophagus should be utilize to obtain control of the bleeding vessels b suturing them.

Technic of Suturing Esophageal Varice The method which is recommended consis in obtaining immediate control of the blee ing esophageal varix by cardio-esophage tamponade with an intragastric balloon.

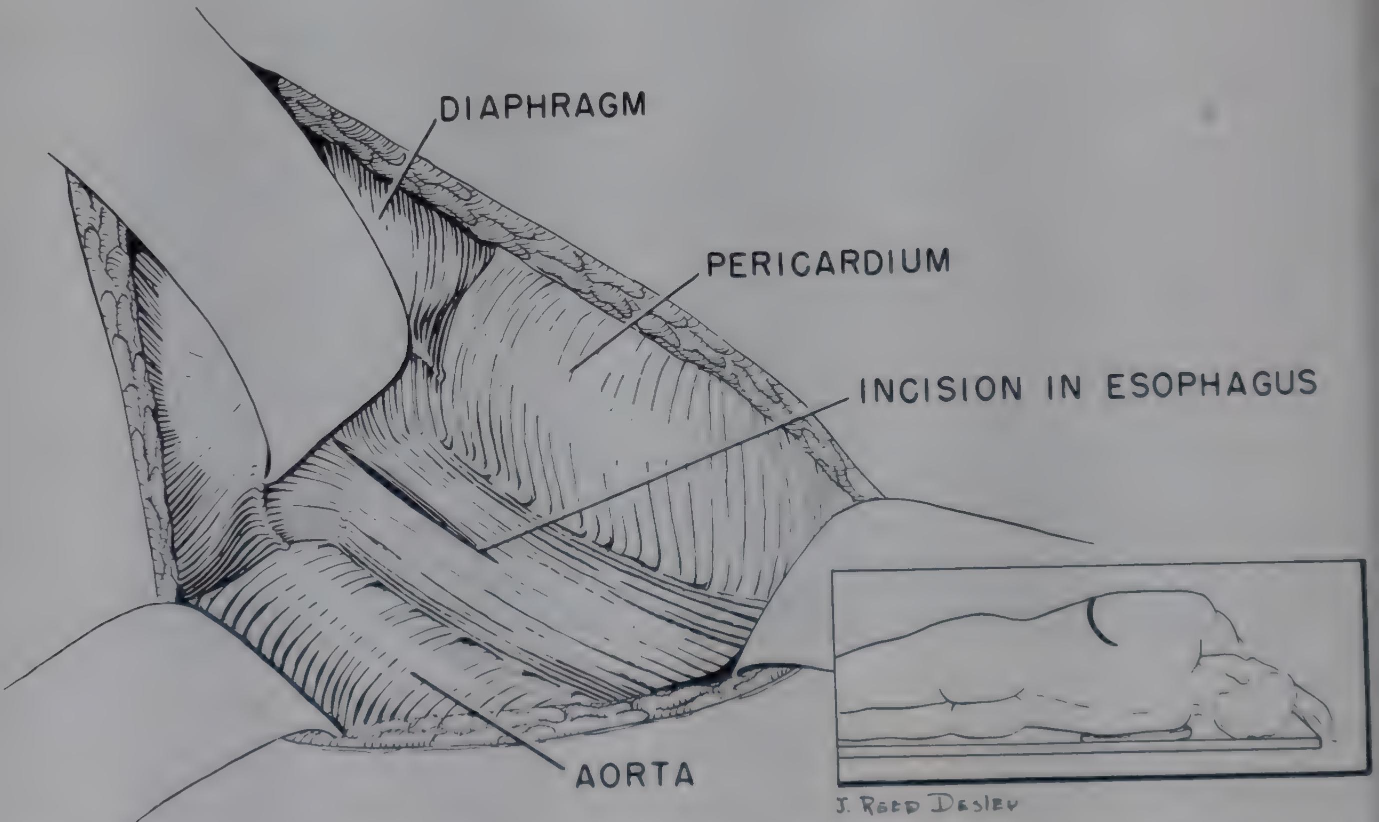


FIG. 71. Demonstration of the exposure of the distal end of the esophagus through a left thoracotomy incision: Note (1) the partial division of the diaphragm to expose the cardia of the stomach; (2) the longitudinal incision in the cardia and the distal end of the esophagus, approximately 5 cm. in length. The inset shows the position of the patient on the operating table and the location of the incision through which the seventh rib is removed in order to open the left pleural space. (Linton, R. R., and Warren, R.: Surgery 33:243-255)

od working rule is that transthoracic nsesophageal exposure and suture of the rices should be performed within 24 hours practically all cases in which it is neces- y to resort to cardio-esophageal tamp- ade to control the esophageal hemorrhage.

After the balloon tube is in place and the eding is controlled, the blood volume ould be restored to near normal by means multiple transfusions. This can be carried t while the operating room is being pre- red for the emergency operation which ould be performed without delay, pro- led that the patient's condition will war- nt it. In many instances it can be per- rmed within a few hours after the patient s been admitted to the hospital.

Cyclopropane is the anesthetic of choice. should be administered through an endo- cheal tube with an inflatable rubber cuff which is inserted after local cocainization of the throat and the larynx, before the general anesthetic is administered, to prevent aspiration of blood during the induction. Traction should be maintained on the balloon tube during the induction period to prevent further bleeding.

The patient is placed in the right lateral decubitus position. The left pleural space is opened by resecting the seventh or the eighth rib subperiosteally. A small incision is made in the diaphragm at the esophageal hiatus to permit exposure of the upper portion of the stomach and the lower end of the esophagus. An incision approximately 5 cm. in length is made in a longitudinal manner equally in the stomach and the esophagus (Fig. 71). The esophageal varices are found frequently to fill the entire lumen of the esophagus similar to the appearance of large

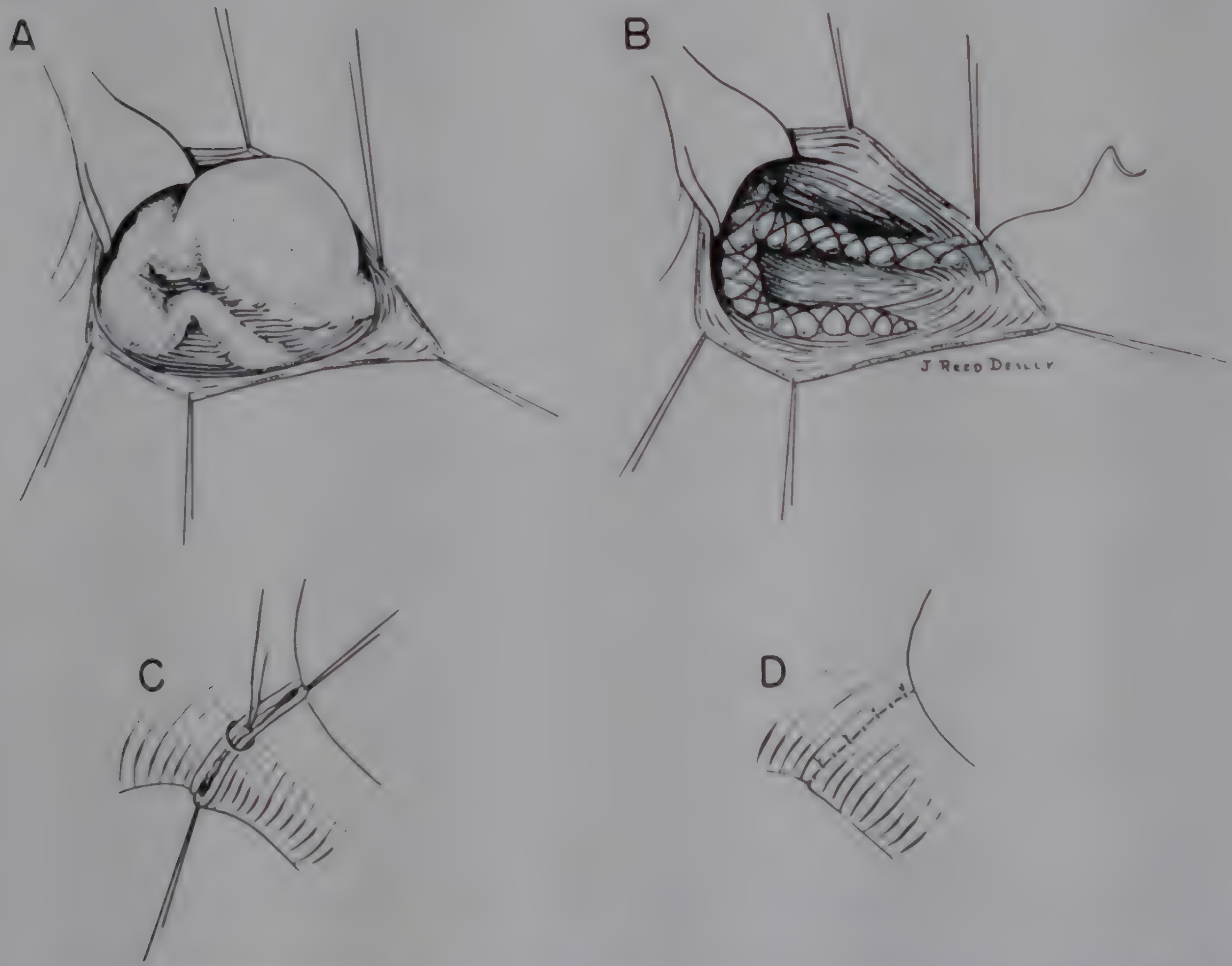


FIG. 72. Demonstration of the technic of transesophageal suture of esophageal varices in the distal end of the esophagus and the varices in the proximal end of the stomach. (A) Huge varices protruding through the gastro-esophageal incision. (B) The collapsed columns of varices after suture with a running over-and-over No. 00 chromic catgut suture. (C) The longitudinal incision is closed transversely with fine interrupted inverting silk sutures. (D) The closure is completed, using 3 layers of fine interrupted silk sutures. (Linton, R. R., and Warren, R.: Surgery 33:243-255)

hemorrhoids in the anal canal, in some instances measuring as much as 1 cm. in diameter (Fig. 72). The actual site of rupture in some cases has been visualized.

The method of suturing these varices consists in elevating the varix with the mucosa covering and obliterating it with a running over-and-over suture of No. 00 chromic catgut on an intestinal needle, carrying it down to and including a portion of the gastric mucosa and the varices in the submucosa of the stomach and then running it up the esophagus for a distance of 4 to 6 cm. As a rule it is possible to isolate 3 columns of varices, and each is sutured in this manner. It is possible by this method to create a block of 8 to 10 cm. in length in this venous system and at the same time control the actual bleeding source. The esophageal varices usually extend much more cephalad than can be sutured, but after adequate suturing it will be noted that the esophageal varices above the area of suturing will have collapsed.

A reduction in the venous pressure in the esophageal varices after suturing them —in one case from 30 cm. to 10 cm. of saline, is contributory evidence that blood in the esophageal varices, as well as that which escapes from them, comes directly from the submucosal veins of the cardia of the stomach. The longitudinal cardioesophageal incision is closed in a transverse manner with 3 rows of fine interrupted silk sutures. Primary healing of it without fistula formation has been attained in all cases. An empyema complicated the convalescence of one patient (Fig. 72).

The results in 20 patients with cirrhosis of the liver with massive hemorrhage from esophageal varices, treated by immediate transthoracic transesophageal suture of these bleeding vessels, have been very encouraging since it has been possible to save the lives of 17, and at a later date perform some type of portacaval shunt. One patient died in the immediate postoperative period, an operative mortality of 10 per cent from liver failure, and the other 2 succumbed 6 weeks postoperatively from the same condition. In the remaining 17 it was possible to build up their general nutrition and blood so that satisfactory shunts were constructed at later dates. The suture technic of controlling t bleeding esophageal varices is not a defin tive form of therapy, because recurre bleeding has been observed a few mont after the procedure in some of the patien that were being prepared for shunt proc dures. For this reason it is recommend now that the shunt be performed as soon possible, preferably within a period of 4 6 weeks after the varices have been suture provided that the patient's general conditi has improved sufficiently to withstand t shunt procedure. It is believed that th method is a life-saving procedure in the critically ill patients (1) because it sav them from dying of hemorrhage and (2) permits time for maximal improvement that the construction of a shunt can be p formed with minimal operative risk.

DEFINITIVE TREATMENT OF BLEEDIN ESOPHAGEAL VARICES

The treatment of portal bed block in presence of esophageal varices should surgical. Patients with cirrhosis of the li unfortunately cannot always be subjected this major type of surgery because of th poor metabolic condition, the result of severely diseased liver. However, by medi means the majority of patients can be p pared satisfactorily so that shunt surg may be performed with a minimum risk. the present state of our knowledge rega ing the therapy of portal bed block, the ch concern is the prevention of hemorrh from the esophageal varices. This compli tion in the intrahepatic or cirrhotic grou frequently lethal, due to exsanguinat hemorrhage. In the extrahepatic group. though the mortality rate is lower from he orrhage, the morbidity is extremely high.

The high mortality rate in patients w bleeding esophageal varices is generally r ognized and is emphasized by recent sta tics of Ratnoff and Patek,[38] and Shull.[39] T latter analyzed a group of 141 patients— with cirrhosis of the liver and 22 with so-called Banti's syndrome or extrahep portal bed block—that were admitted to Massachusetts General Hospital during years 1934 to 1945 inclusive. Bleeding fr the esophageal varices was a serious sy tom in many of these patients. They were

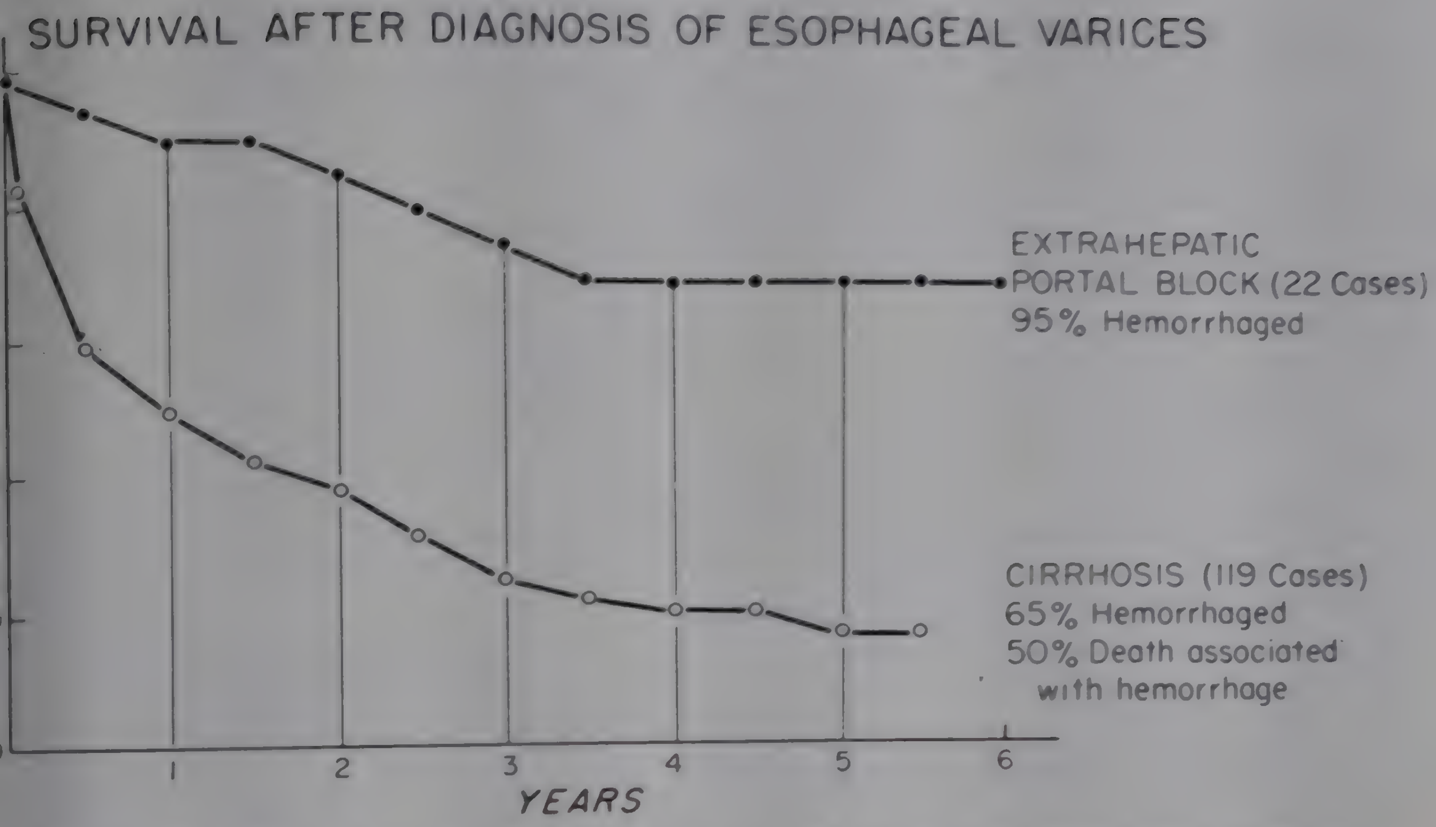


FIG. 73. The survival rates after the diagnosis of esophageal varices was made in
19 patients with an intrahepatic portal bed block and in 22 patients with an extra-
epatic block seen at the Massachusetts General Hospital from 1934 and 1945 and
reated by conservative measures without the benefit of shunt surgery. (Merendino,
K. A., and Volwiler, W.: Northwest Med. 52:724, and Shull[39])

d conservatively, except in a few in-
es of extrahepatic block in whom sple-
my alone was performed. The over-all
lity in these 141 patients over the pe-
studied revealed that 97 (69%) of the
nts died from all causes. Exsanguina-
secondary to rupture of the esophageal
es was the cause of death in 46 (47%)
e deaths, and in many of the other
atients who died, bleeding from these
ls played a major contributory role.
death rate from bleeding esophageal
es in the patients with cirrhosis of
iver was much higher than in those
the extrahepatic block, since in a
of 71 patients with the former disease
bleeding esophageal varices, 16 (23%)
died at the end of 1 month; 29 (41%)
6 months; and 38 (54%) had suc-
ed at the end of 1 year; whereas in 19
nts with the extrahepatic type of block
1 (5%) had succumbed at the end of 1
(Table 12). These figures demonstrate
ly that bleeding from the esophageal
es is much more serious in patients with
osis of the liver than in the younger
age group with extrahepatic block and an essentially normal liver. It is of interest also that Shull[39] found that the mortality rate after the diagnosis of esophageal varices had been made in patients with cirrhosis of the liver, with or without bleeding from them, was 50 per cent at the end of 1 year and 78 per cent after 4 years. On the other hand, he found that the life expectancy in patients with the extrahepatic block was much better,

TABLE 12. MORTALITY AFTER HEMORRHAGE FROM ESOPHAGEAL VARICES
Massachusetts General Hospital (Dr. H. J. Shull), 1934–1945, Inclusive

	71 PATIENTS		19 PATIENTS	
	Cirrhosis Died		*Banti's Died*	
1 mo.	16	23%	1	5%
6 mo.	29	41%	1	5%
12 mo.	38	54%	1	5%
2 yr.	46	65%	1	5%
4 yr.	55	77%	5	26%
7 yr.	58	82%	8	42%

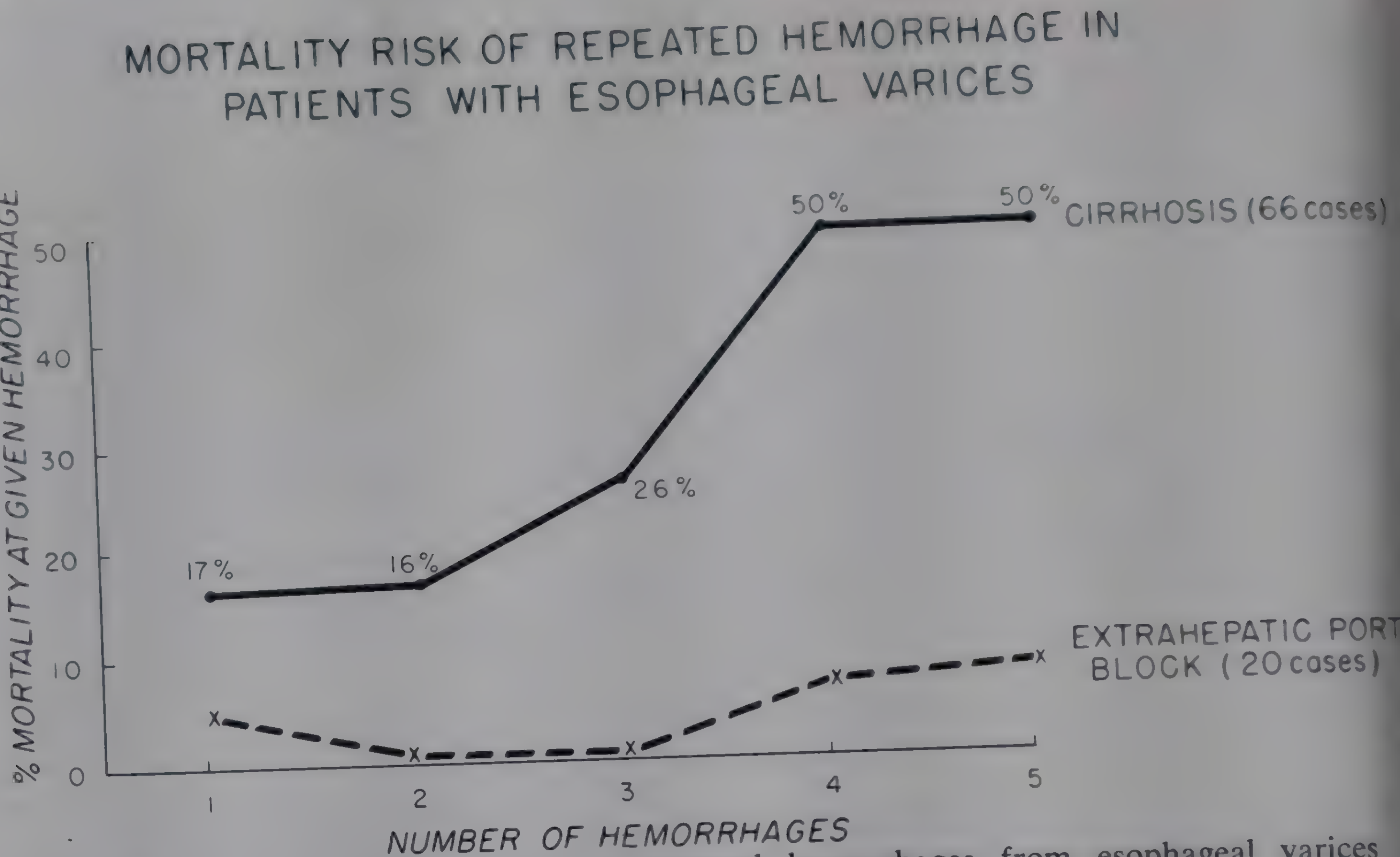


FIG. 74. The mortality risk of repeated hemorrhages from esophageal varices observed in 66 patients with an intrahepatic portal bed block and 20 patients with an extrahepatic block, taken from the records of the Massachusetts General Hospital from 1934 and 1945. (Merendino, K. A., and Volwiler, W.: Northwest Med. 52:724, and Shull[39])

since 90 per cent were alive at the end of 1 year, and 70 per cent at the end of 4 years (Fig. 73). He also found that the mortality risk of repeated hemorrhages was very grave in those patients with cirrhosis of the liver, since in 66 cases, 11 (17%) of them died following the first hemorrhage, and the mortality rate increased to 50 per cent in those who had bled for the fourth time. The mortality was not nearly so great in 20 cases of the extrahepatic block, even though these patients had repeated hemorrhages, since it was between 5 and 10 per cent after repeated hemorrhages over a 4-year period of follow-up (Fig 74). In addition to this high mortality rate, the morbidity of the disease in each group is extremely high, since long hospitalization is necessary with numerous blood transfusions to replace the blood that is lost. It is obvious from these statistics that it is extremely important that some form of treatment be developed to prevent further bleeding from these esophageal varices.

Many surgical procedures have been performed and recommended during the past half century. It is generally recognized that medical measures have little value in co trolling or preventing this type of hem rhage. The surgical methods of treatme that have been advocated may be divid into 5 headings: (1) methods to reduce t arterial inflow to the portal bed; (2) me ods to increase the collateral circulation b tween the portal and the systemic veno systems; (3) methods to reduce the veno blood flow into the esophageal veins; (methods to control the esophageal varic (5) methods to shunt the portal blood rectly into the systemic venous system.

Methods to Reduce the Arterial Inflow the Portal Bed

INTERRUPTION OF THE SPLENIC ARTE It is generally understood that the sple arterial blood constitutes approximately to 40 per cent of the total amount of arte blood entering the portal bed, the act amount depending on the size of the sple The larger this organ is, the greater will the blood flow through it. Interruption of splenic artery is recommended by vari authorities[5, 12] in order to reduce the arte inflow into the portal bed, thereby reduc

ortal venous pressure and the danger of
ure of the esophageal varices. The re-
of this method of treatment have not
encouraging. In our clinic in 8 splenic
y interruptions, 6 (75%) of the pa-
s had secondary severe hemorrhages
which 3 (38%) died. At one time it
recommended by us as a first-stage pro-
re to control the bleeding esophageal
ces, but it was useful only in a few in-
ces and chiefly in those that were bleed-
nly a slight amount rather than in those
massive hemorrhage. Because of these
results, this method has been aban-
ed in our clinic.

PLENECTOMY has been, until recent
s, the most commonly employed surgi-
method to control the bleeding esophag-
varices, especially in those patients with
extrahepatic portal bed block. The
nale of this procedure is essentially
same as that of ligation of the splenic
y except that, in addition, it may rem-
temporarily the marked anemia, leuko-
a and thrombocytopenia, the blood
ges characteristic of congestive spleno-
aly or hypersplenism. Despite this im-
ement which may take place in the blood
re, it is believed that any benefit derived
eby is offset by the fact that numerous
us collateral anastomoses between the
al bed and the systemic venous system,
ugh the multitudinous small blood ves-
which develop in the attachment of the
en to the diaphragm and the posterior
oneum, necessarily are all severed when
spleen is removed. For this reason it is
idered a serious mistake to perform a
ectomy alone. In addition, splenectomy
ts in thrombosis of the proximal end of
plenic vein, so that at a later date it will
npossible to construct a splenorenal or
type of portacaval anastomosis in the
hepatic type of portal bed block, be-
e frequently in these patients there is a
rnomatous change about the portal vein
prevents its surgical exposure. No sta-
s are available to demonstrate the in-
tiveness of splenectomy alone in the
ment of portal hypertension, but it has
me obvious to those who work in this
that the majority of patients continue
eed following this procedure, so that in
our present state of knowledge the operation is to be condemned and should be abandoned.

INTERRUPTION OF THE HEPATIC, THE SPLENIC AND THE LEFT GASTRIC ARTERIES. This method has been advocated for the treatment of bleeding esophageal varices secondary to an intrahepatic type of block,[4, 34] because it lowers temporarily the state of portal hypertension to a slight extent by reducing the amount of blood flow entering the portal area, and, in addition, interruption of the hepatic artery reduces the intrahepatic blood pressure so that the portal venous blood may make its passage more readily through a cirrhotic liver. However, experience has demonstrated that this type of multiple blood vessel interruption does not produce permanent relief from portal hypertension or relief from hemorrhage from the esophageal varices, undoubtedly because the arterial inflow to the portal bed is reestablished by an increase in the caliber of the collateral arterial channels. In addition, the mortality rate from the procedure is too high to warrant its continuance, as many of the patients die from hepatic failure due to liver necrosis. A recent report[4] also reveals that only 30 per cent of a group of patients with cirrhosis of the liver treated by this method were alive at the end of 1 year, a higher mortality than the medically treated cases. In summary, then, it can be stated that the methods used to reduce the arterial inflow to the portal bed are of little or no value in the therapy of portal hypertension; for that reason it is believed that they should be abandoned.

Methods to Increase the Collateral Circulation

OMENTOPEXY OR TALMA-MORISON OPERATION. It has been recognized for many years that the portal systemic venous collateral circulation in patients with a portal bed block has a limited capacity, so that various methods have been devised in an attempt to augment it. The first of these was described in the latter part of the last century. The original technic, as described by Talma[42] and simultaneously by Morison,[12] consisted in placing the omentum between the liver and the diaphragmatic peritoneum after roughening the surfaces of these two structures so that new vascular channels would form between the portal bed, the liver and the parietal peritoneum. Modifications of this procedure appeared in the surgical literature for a number of years later. Many patients have been subjected to these different types of operative procedures in the past, but it can be said truthfully that only a rare patient has been benefited by them. As a result, they have been discontinued and abandoned almost universally. The chief benefit, if any, derived from them was not in the control of bleeding from the esophageal varices but in the control of the formation of ascites. In retrospect, however, even for the treatment of this complication of cirrhosis, there seems to be considerable doubt that omentopexy, or similar procedures, played much if any role in the relief of the ascites, since the formation of it for the most part is due to a chemical derangement in the body rather than to a vascular mechanical one, because of an increase in the portal venous pressure. It seems more likely that it was the natural course of the disease, since in some individuals, ascites disappears spontaneously with the improvement in liver function.

ANOTHER SIMILAR METHOD has been reported by Garlock[40] to improve the collateral circulation between the esophagus and the mediastinum and the thoracic wall. It consists in opening the superior mediastinum and packing it with a long strip of gauze through a supraclavicular incision, then removing it gradually, beginning in a few days after an inflammatory process had been set up by this foreign body. In view of the fact that this procedure is carried out in the upper portion of the thorax, it seems doubtful that sufficient blood can be shunted from the esophagus into the systemic venous system by this rather novel approach to the problem. Similar to the other methods of developing a collateral circulation, this one also has been abandoned by the majority of workers in the field. In summary, it can be stated that the theory of these procedures is a rational one, but, unfortunately, none of the methods produces large enough vascular channels to permit sufficient blood to bypass the portal bed block to reduce the state of portal hypertension.

Methods to Reduce the Flow of
Venous Blood into the Esophageal V
In the past various attempts have bee
to reduce the blood flowing into th
phageal varices by ligation of various
taries of the portal venous system
were thought to feed these blood vess

INTERRUPTION OF THE CORONARY
The first of these methods was repo
1939 by Walters and Rowntree.[44]
sisted of interruption of the coronary
the stomach and the venous tributarie
region of the cardia through a transa
nal exposure. The ineffectiveness
method was soon demonstrated bec
continued bleeding in many patients

LIGATURE OF PERIESOPHAGEAL
The next attack was made through th
ral cavity, and an attempt was made
rupt all the periesophageal venous
that could be found through a tran
exposure. This method also proved t
effective. Neither of these proced
based on sound vascular principles
the source of blood feeding the eso
varices was not interrupted, but ins
outflow from them was, in part at
that both of these methods probably
portal venous stasis rather than re

TRANSECTION OF CARDIA OF S
A more recent attempt to interrupt
vessels feeding the esophageal var
been reported by Tanner.[43] He has
mended transection of the cardia
stomach a few centimeters from the
esophageal junction through a trans
nal exposure. Since blood enters
phageal varices, for the most part,
large gastric submucosal plexuses
this procedure is a rational one a
porary method of control because
rupts the blood flow to them for
part. Unfortunately, since the port
tension is not affected, it is not a
procedure, and it is not long be
venous channels have redevelope
the line of suture where the transec
performed, and the esophageal vess
become engorged and bleed. It prob
value only as an emergency proce
method to control massive blee
esophageal varices when other met
failed.

OGOGASTRECTOMY. A somewhat pproach to the problem has been by Phemister[40] who recommended agogastrectomy. This procedure, of ot only interrupts the venous chan- ing the esophageal varices but also ome of them and, in addition also, he varices themselves. This method to considerable criticism, however, of the magnitude of the procedure fact that the state of portal hyper- s not affected, so that nature again w venous channels to feed the re- esophageal varices which then bleed

GASTRECTOMY. Complete resec- e stomach has been recommended gensteen[2] and Phemister.[40] The elieves that the benefits of such a e consist chiefly in removing the etion of the stomach which may re- up the esophagus and set up a lceration of the esophageal mucosa ion of the esophageal varices and age from them. There is consid- oubt over this hypothesis, and it ore likely that the benefit derived al gastrectomy consists in interrupt- eins that feed the esophageal varices, me time partially reducing the portal sion by reducing the portal inflow nount of blood that ordinarily passes the stomach. At the present time it ht that this procedure is the one of rt and even then, unfortunately, it is re because the state of portal hyper- s affected for a short time only, so remaining varices dilate later as new form again to connect the portal ystem with them. It should be re- ed also that the ill effects resulting alnutrition following total gastrec- ay outweigh the benefits that may m such a radical procedure.

Methods to Control Bleeding eal Varices

OSING ESOPHAGEAL VARICES. Con- eeding esophageal varices by obliter- em with a sclerosing solution was orted by Crafoord[9] in 1939, after g them through an esophagoscope. thod of treatment was in vogue for r of years but has been abandoned by the majority because of the ineffectiveness of the procedure, and because it is almost impossible to sclerose the varices at the lower end of the esophagus where bleeding, in the vast majority of cases, occurs. In addition, the procedure has seemed to initiate severe bleeding in a number of instances. Furthermore, the treatment probably results only in a venous thrombosis rather than sclerosis of the varices so that recanalization undoubtedly takes place, and the benefit, if any, to be derived is of relatively short duration.

SURGICAL. Methods to control bleeding esophageal varices by a direct surgical attack on them have been developed only recently because of the location of the esophageal varices and their relative inaccessibility. With the advances that have been made in thoracic surgery, the ability to replace large amounts of blood quickly, and the improvements in anesthesia, it has been possible in recent years to control the esophageal varices by suturing them, even at the time of acute bleeding, by exposing them through a transpleural transesophageal exposure. Boerema,[4] in 1949, and Crile,[10] in 1950, recommended this method as a definitive procedure. It is believed, however, that it should be used chiefly as an emergency form of treatment to control the ruptured esophageal varices, thereby saving the patient from exsanguination. Like most of the other methods that have been described above, this procedure in no way influences the state of portal hypertension. In our experience with this type of treatment, the esophageal varices reform with recurrent esophageal hemorrhages, especially in patients with cirrhosis of the liver, often within a matter of a few months.

Methods to Shunt the Portal Venous Blood into the Systemic Venous System. A Russian physiologist, Eck,[14] in 1877, published the first report of shunting the portal blood directly into the inferior vena cava by what is now known as an Eck fistula. He carried this out on an experimental basis in animals to study the effect of it on the liver and the general metabolism. However, he suggested that such a portacaval fistula might be used to bypass an obstruction in the portal vein.

According to Whipple,[46] the procedure was not carried out until Tansini[47] advocated it in 1902. Vidal[47] claimed to have been the first to do the operation in 1903 on a patient with portal obstruction. Unfortunately, this patient only lived 14 weeks, dying of a septic phlebitis. DeMartel[47] performed a successful Eck fistula on a patient in 1910, but the patient succumbed shortly afterward from anuria. Rosenstein[47] performed the procedure in 1911 on a 60-year-old woman with cirrhosis of the liver and ascites and demonstrated that 5 months after the Eck fistula had been performed the ascites was reduced considerably in amount, so that only an occasional paracentesis was required. Undoubtedly, many other patients were subjected to this procedure, but few have been recorded in the literature.

Other types of venovenous anastomoses between the portal and the systemic venous systems have been attempted. These include an anastomosis between the right ovarian and the portal veins by Gunn[47] in 1911; one between the ovarian and the superior mesenteric veins by Villard and Tavernier[47] in 1914. Meursing,[47] in 1912, reported anastomosing the spermatic vein to the splenic vein without success; and Bogarts,[47] in 1913, successfully anastomosed the superior mesenteric vein to the inferior vena cava. Unfortunately, the follow-up on this latter patient is only 1 month, so the long-term effect of the procedure is not known. Eck fistulae have been carried out in experimental animals by many investigators.

George H. Whipple[48] has had as much experience probably as any one in this experimental study on dogs. He studied some of them for as long as 8 years in an apparent state of good health. He found that the blood supply of the hepatic artery is adequate in these animals to support relatively normal liver function for many years, provided that their diet is not too high in proteins.

McDermott[27] has noted recently that a few patients developed protein intoxication after portacaval shunts and that it may be detected in some by measuring the ammonia level of the blood. Fortunately, however, the number of patients seriously affected in this manner is small, so that for the most part, the possible development of this type of syndrome has not been a deterrent to the use of portacaval shunts in the treatment of bleeding esophageal varices. It seems to oc
more frequently after direct anastomosis
tween the portal vein and the inferior v
cava, in patients with severely dama
livers, than when a splenorenal shunt is p
formed under similar conditions.

During the past decade there has bee
renewed interest in the construction of v
ous types of portacaval shunts between
portal venous and the systemic venous
tems for the treatment of bleeding esophag
varices. This has come about chiefly beca
of the encouraging results in a group
patients reported in 1945 by Whipple[46]
Blakemore.[6] They first recommended rem
ing the spleen and the kidney, then
forming an end-to-end anastomosis betw
the splenic and the renal veins, or a di
end-to-side anastomosis between the po
vein and the inferior vena cava, using
vitallium tube technic of Blakemore. Un
tunately, with this technic thrombosis
veloped at the site of anastomosis i
number of cases, so that newer technics
more satisfactory venovenous anastom
have been developed. These include
end-to-side type of anastomosis by the su
technic between the cut end of the spl
vein and the side of the renal vein, after
forming a splenectomy; it was first repo
in 1947.[23] In addition to reducing the
dence of thrombosis by this type of shunt
left kidney is also preserved, which ma
of extreme importance in some of the
ill patients. Also, the suture technic for a
tomoses between the portal vein and
inferior vena cava, either end-to-side or
to-side, has been adopted successfully.

A careful follow-up of cases that
done early in this study, some of which
been cured of their bleeding esoph
varices for 7 to 9 years, clearly demonst
that these 3 types of portacaval shunts
the best available methods of treating p
hypertension with bleeding esophageal
ces. Other types of venovenous anaston
have been used, but mostly as a last r
in the postsplenectomy bleeder in whon
portal vein cannot be isolated because c
cavernomatous change around it.

One of these is to anastomose the sup
mesenteric vein to the inferior vena
(Fig. 75). The former is divided at the

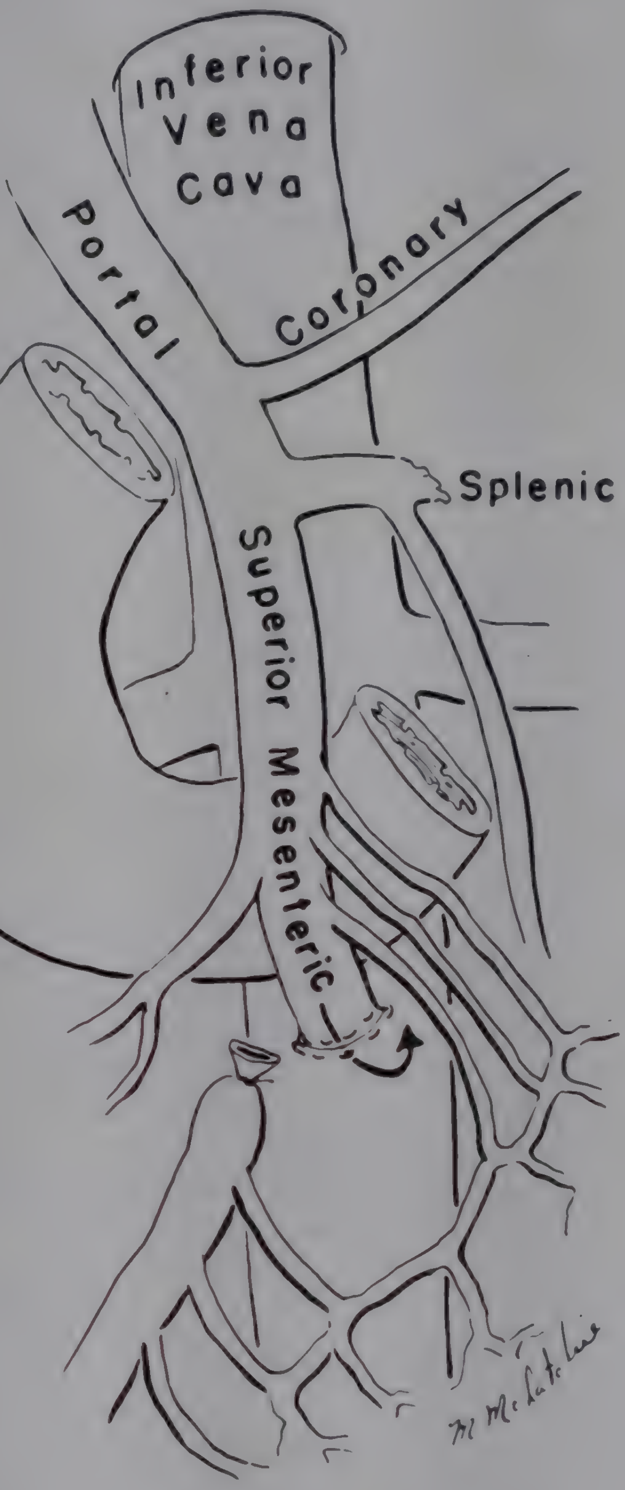


FIG. 75. Direct anastomosis between
e proximal end of the divided superior
esenteric vein and the inferior vena
va. This type of shunt has been utilized
th relief of bleeding for a patient in
nom the splenic vein could not be uti-
ed because of a previous splenectomy,
d the portal vein could not be exposed
cause of a cavernomatous change sur-
unding it. It is not always possible to
nstruct this type of shunt, and it is not
good a one as the splenorenal or the
rect portacaval types, but in this patient
has functioned satisfactorily for 10
ars.

e mesentery, and the proximal end is
ed by an end-to-side anastomosis to the
ior wall of the inferior vena cava. In
uccessful case, the patient has survived
oximately 10 years following the shunt.
veral attempts also have been made to
omose the inferior mesenteric vein to
r the ovarian or the renal vein, but these
not been successful because of the rela-
small size of these portal venous
les, so that it is felt that they should be
doned.

akemore has advocated recently a ve-
graft between the stump of the splenic
and the renal vein in the postsplenec-
bleeder. Unfortunately, this procedure
t feasible in most of these cases because
e impossibility of isolating the stump of
plenic vein. However, it is a method
should be attempted before resorting to
ess definitive procedures of esophago-
ectomy and total gastrectomy.

summary, it can be stated that some
of portacaval shunt is the only method
educes portal hypertension satisfactorily
unting a sufficiently large volume of the
l blood directly into the systemic venous
n, thereby lowering the venous pressure
e esophageal varices and so preventing
re of them.

THE MOST EFFECTIVE TYPES OF PORTACAVAL SHUNTS

e anastomosis of the portal venous sys-
o the systemic venous system by various
of venovenous shunts fell into disrepute
g the first part of this century because of
lmost universally poor results obtained
in the patients operated upon. This was due in part to the fact that the operation was performed for the treatment of ascites, which we now believe, in the majority of cases, is a contraindication to shunt surgery. It was not until 1945 that Whipple[46] and Blakemore[6] reported encouraging results following a new attack on the problem by utilizing the nonsuture method of vascular anastomosis as developed by Blakemore, and also introducing the splenorenal type of shunt. Many others[7, 19, 20, 25, 28, 45] have followed their lead with excellent results in the hands of surgeons well trained in the field of vascular surgery. This improvement in results as compared with the earlier attempts in this century is

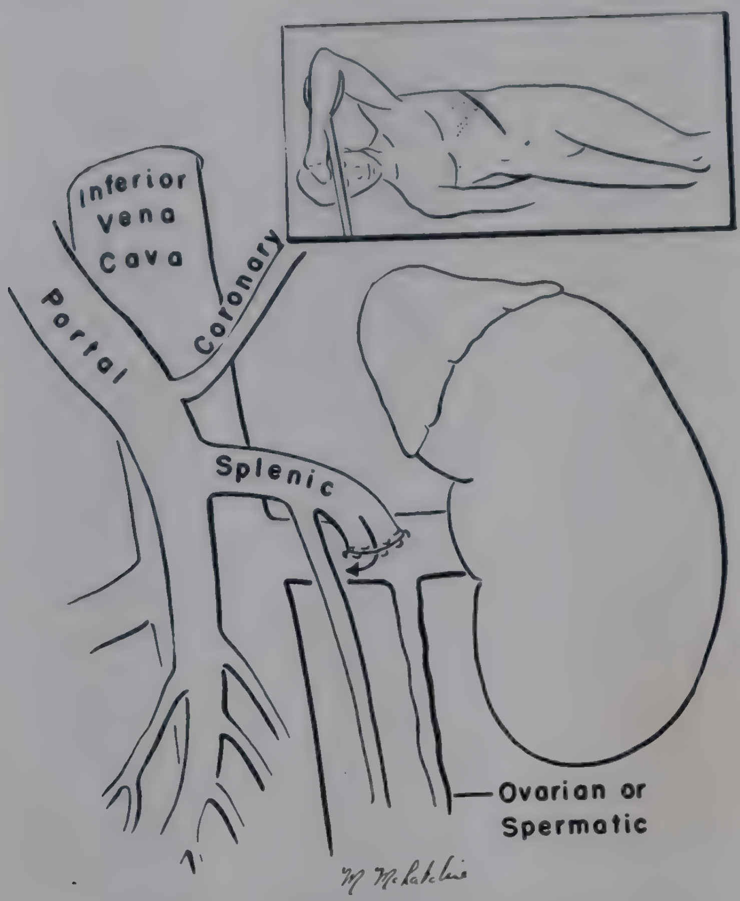


FIG. 76. End-to-side splenorenal shunt between the proximal end of the splenic vein and the side of the renal vein, after performing a splenectomy. An ellipse of the renal vein is excised in order to make a wider stoma. It is constructed with a running mattress suture of fine (5-0) silk, everting the edges in order to have an intima-to-intima approximation of the two veins. This method of suturing cannot be overemphasized in venovenous anastomoses in order to prevent thrombosis because of the relatively slow rate of blood flow through veins. The inset demonstrates the patient in the 45° right decubitus position on the operating table and the location of the thoraco-abdominal type of incision.

due to a number of factors, which include: (1) a better understanding of the pathologic physiology of the severely damaged liver so frequently encountered in many of the cirrhotic patients, which permits better preoperative preparation and postoperative care of the patients; (2) improvements in surgical technic, along with better instruments and suture materials with which to construct shunts; (3) the establishment of the modern blood bank to make available adequate transfusions during these long operative procedures; and (4) the great improvements in
anesthesiology which have made it possil
not only to operate on these patients w
severely damaged livers but also for ma
hours without serious deleterious effects.

The following types of portacaval shu
are the ones most commonly performed:

An End-to-side Splenorenal Shunt w
Splenectomy (Fig. 76). This type of ope
tive procedure has been performed in
clinic more frequently than any other.[23] It
the advantage that in removing the spl
the condition of hypersplenism is correc
which frequently is found secondary to
portal bed block, of either intrahepatic
extrahepatic type. In the majority of ca
it is thought to be a safer operation than
direct portacaval anastomosis, since there
less danger of damaging such vital structu
as the hepatic artery or the common bile d
which lie in such close proximity to the po
vein. Nevertheless, it is the more difficult t
of venovenous anastomosis to perform,
cause the splenic vein frequently is found
be extremely fragile, and the small pan
atic branches that drain into it may be t
resulting in much trouble in controlling th

At the present time it is our working
that if there is a marked splenomegaly,
enlarged splenic vein will be found in
majority of cases with which it is possibl
construct a satisfactory shunt. On the o
hand, if the spleen is small, both by palpa
and by x-ray examination, the splenic vei
frequently too small to make a well-funct
ing shunt, so that in these cases it is ele
to perform a direct portacaval anastom

In the patients with the extrahepatic
of block, the splenorenal shunt is with
question the operation of choice becaus
most of these patients, the portal vein ca
be exposed because of the cavernoma
change in the gastrohepatic ligament
rounding it. The chief drawback to
splenorenal shunt is that it may not be
sible to make it large enough to shunt
cient blood. As evidence of this is the
that the majority of secondary hemorrh
following shunt surgery have occurred in
tients with splenorenal anastomoses.
on the other hand, is somewhat cou
balanced by the fact that patients with
norenal shunts do not seem to develop
serious liver complications that are seen

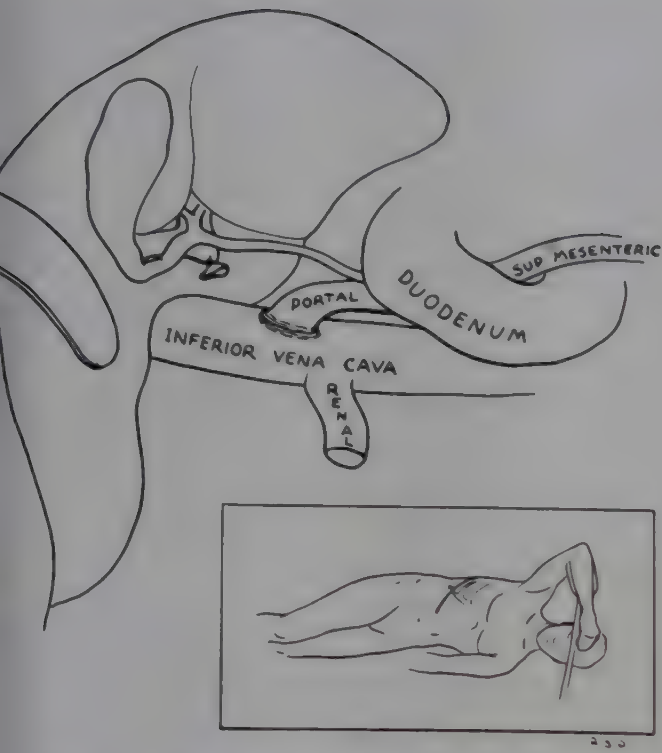


Fig. 77. End-to-side direct anastomosis
etween the distal end of the divided por-
l vein and the anterior side of the in-
rior vena cava. This is constructed with
running everting type of fine silk suture
milar to the splenorenal anastomosis.
he inset demonstrates the patient in the
ft decubitus position at a 90° angle on
e operating table, and the location of the
oraco-abdominal type of incision. This
the preferred type of direct portal vein-
-inferior vena cava anastomosis.

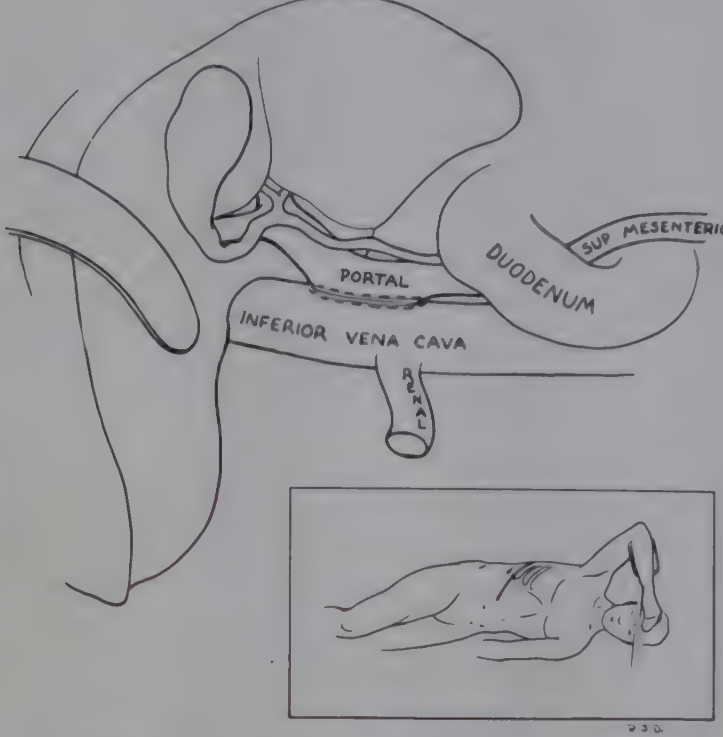


Fig. 78. Side-to-side direct anastomosis between the portal vein and the inferior vena cava without dividing the portal vein. This type of shunt is not recommended in patients with a high degree of intrahepatic portal bed block because the liver, for the most part, is deprived of the hepatic arterial blood as well as the portal venous blood, since both are shunted through the anastomosis. The inset shows the patient in the left 90° decubitus position, and the thoraco-abdominal type of incision.

quently following the direct portal vein
nferior vena cava anastomosis.
general, it is believed that the end-to-
splenorenal anastomosis with splenec-
y is the operative procedure and the type
hunt that should be performed on most
ents with an intrahepatic portal bed
k with an enlarged spleen, and in all
ents with an extrahepatic type of block
have not had a splenectomy previously.
**Direct Portal Vein to Inferior Vena
a Shunt** (Figs. 77, 78). This type of
venous anastomosis in many instances,
cially in patients with cirrhosis of the
, may be constructed more readily be-
e one is dealing with the portal vein and
nferior vena cava, which are larger and
fragile blood vessels than the splenic and
enal veins; furthermore, in this disease
cavernomatous change around the portal
is seen infrequently so that this vessel
may be exposed readily. However, the operative procedure may be fraught with considerable danger because of possible injury to the common bile duct or the hepatic artery because of their close proximity. Furthermore, against this type of shunt there is some evidence accumulating that it results in more serious effects to the liver than the splenorenal type, but further studies along these lines are necessary before drawing definite conclusions.

There are two methods of anastomosing the portal vein to the inferior vena cava: (1) it may be a side-to-side anastomosis without interrupting the continuity of the portal vein (Fig. 78); or (2) an end-to-side anastomosis, implanting the distal end of the portal vein, after ligating and dividing it, into the side of the inferior vena cava (Fig. 77). The former type of anastomosis is not recommended because it is believed that in those patients with an intrahepatic portal bed block, the hepatic arterial blood, as well as the portal venous blood, will be shunted through the portacaval anastomosis, since both will follow the path of least resistance, which is through the shunt, thereby depriving the liver, for the most part, of both its arterial and venous blood supplies. This of course is not true with an end-to-side type of shunt because with it the hepatic arterial blood must pass through the liver and out through the hepatic veins.

The opinion that the side-to-side type permits some of the portal venous blood to pass through the liver seems very unlikely to be true, especially in those patients with a high degree of block, since the blood from the portal vein will follow the path of least resistance, namely, through the shunt into the inferior vena cava rather than through the obstructed venous pathways of a cirrhotic liver. As the degree of portal bed block may vary in different patients, it is possible that in those with the less marked degree, a side-to-side shunt might function satisfactorily, since some of the arterial blood would go through the liver.

However, because it is not always possible to determine how complete the block is, it is recommended that the end-to-side shunt be performed in all the cases because it deprives the liver of a relatively small amount of its portal venous blood supply, due to the existing intrahepatic block of the cirrhotic process, and at the same time the liver is not deprived of its arterial blood supply.

SELECTION OF PATIENTS FOR PORTACAVAL SHUNTS

The construction of portacaval shunts should be reserved for those patients with portal hypertension of either intrahepatic or extrahepatic origin in whom bleeding esophageal varices have been demonstrated. They may be performed also as a prophylactic procedure on patients in whom esophageal varices have been demonstrated without bleeding, but at the present time it is thought best that further time should be allowed to elapse to study and evaluate those patients in whom shunt surgery has been performed for bleeding esophageal varices, since it is obvious that if it does not prev recurrent bleeding in these cases, a sh should not be recommended as a prophyl tic procedure. In defense of portacaval shu it can be said that sufficient data is bei accumulated that seems to demonstrate t the construction of an adequate one will p vent esophageal hemorrhage. Since por hypertension with or without esophag varices manifests itself in a number of d ease complexes, it is possible to class them into the following categories, w recommendations concerning the perfor ance of shunt surgery.

INTRAHEPATIC PORTAL BED BLOCK

Portal Cirrhosis With Bleeding Esoph eal Varices Without Ascites. Patients this group are the most suitable cases shunt surgery, since the occurrence of ble ing from esophageal varices indicates t the life expectancy of the majority of th is probably less than 1 year, and the that ascites is not present indicates that liver is not too severely damaged so that patient will withstand the long and diffi surgical procedure of constructing a sh This type of disease represents the great jority of the patients in the series of cirrh operated upon in our clinic. The absenc ascites as a rule indicates a fairly well c pensated liver from the protein metab viewpoint. Other liver-function tests, inc ing the cephalin flocculation, the quan tive van den Bergh, the prothrombin ti and the serum albumin, are usually wi normal limits. The bromsulfalein reten test may be well above the normal value, apparently this is not a serious contraind tion to surgery if the other tests are relati normal. The good results obtained in group have demonstrated clearly the valu shunt surgery in the prevention of fur bleeding from esophageal varices, so th is recommended especially for this grou patients.

Portal Cirrhosis With Bleeding Esopha Varices With Ascites

WITH CHRONIC ASCITES. This dis complex presents a real challenge to th ternist and the surgeon. The develop of bleeding from esophageal varices in a tient with portal cirrhosis and ascites i emely serious prognostic sign, because, ording to statistics, such a patient has a ter than 50 per cent chance of dying hin 1 year unless a portacaval shunt of e type is performed to prevent further ding. It is of extreme significance, how- r, to realize that if the ascites is chronic long standing, it may be impossible to orm the operative procedure because of technical difficulties that frequently are ountered in such cases. Because of this since the patient will be such a poor rative risk, the result of liver disease and tein imbalance, a shunt procedure is con- ndicated until the ascites is cleared by lical measures. The first step in the prepa- on of this type of patient for shunt surgery uld be to obtain temporary control of the phageal varices so that the medical treat- nt may be carried out without complica- from further bleeding. This is accom- hed by a direct suture of these vessels ough a transthoracic transesophageal ex- ure. Then it will be possible to improve liver function and build up the serum umin level, utilizing, if necessary, intra- ous injections of human albumin. After ximum improvement has been obtained, ch may take several months, the second- ge procedure should be the construction either a direct portacaval shunt or an end- side splenorenal shunt with a splenectomy.

WITH ACUTE ASCITES. Ascites may de- op suddenly following a massive hemor- ge from the esophageal varices due to the ering of the serum protein and albumin els with a resulting drop in the blood's notic pressure. In contradistinction to the ients with chronic ascites, these respond atively soon to an adequate medical regi- n, if the bleeding ceases or is controlled the suture technic, and shunt surgery can performed after a relatively short period preparation.

Portal Cirrhosis With Esophageal Varices thout Bleeding. Frequently, the diagnosis esophageal varices is not made without a tory of hematemesis or melena, since most the patients seek medical and surgical at- tion only after a severe bout of bleeding. wever, esophageal varices are demon- ated not infrequently during the study of patient with cirrhosis of the liver. At the present time it is not the policy in our clinic to operate upon these patients until we have demonstrated more clearly that shunt surgery will prevent further bleeding in those cases that have had esophageal hemorrhages. As our experience increases and the mortality rate of the operation is kept at a reduced rate, it is probable that shunt surgery will be recommended in such cases as soon as the value of it is proved without question in a large group of cases with a previous history of esophageal bleeding.

Portal Cirrhosis With Ascites and Without Esophageal Varices. There are many patients with portal cirrhosis and chronic ascites but without esophageal varices. In the past they have been treated by repeated abdominal paracenteses and medical therapy. It was the hope, and it is still the erroneous belief, of many physicians and surgeons that the ascites might be controlled or prevented by reducing the portal venous pressure by the construction of a portacaval shunt. Unfortunately, however, portal pressure is only one of the factors[49] in the formation of ascites, and it is probably of much less importance than the serum albumin and electrolyte levels which are not affected by the construction of a shunt. It is of interest, also, that following the construction of a satisfactory shunt in patients with minimal ascites, massive ascites has developed in some patients after the shunt has been constructed, indicating that even a satisfactory venovenous anastomosis does not prevent or control the formation of ascites. Therefore, it can be stated categorically that shunts should not be attempted in this group of patients.

Portal Cirrhosis Without Esophageal Varices and Ascites. Although accurate statistics are not available, there are a number of instances in which a diagnosis of portal cirrhosis is made without ascites, and roentgenologic examination of the esophagus fails to reveal the presence of esophageal varices. Confronted with such a patient, it is believed that at the present time there is no indication for the construction of any type of portacaval shunt. The absence of esophageal varices, it is believed, indicates little, if any, portal hypertension. Furthermore, there is little evidence, if any, that a shunt improves the function of the liver. Therefore, in the absence of bleeding esophageal varices, it is believed that this group of patients should not be considered as candidates for this type of surgery, and for that reason medical measures should be resorted to.

EXTRAHEPATIC PORTAL BED BLOCK

The cause of the extrahepatic type of portal bed block, in most instances, is due to a thrombosis of the portal vein or its main radicles or a congenital obliteration of it. As a rule, the splenic vein does not become thrombosed until late in the course of the disease. The condition may develop early in life, it is believed, as a result of omphalitis, with secondary thrombosis of the ductus venosus and extension of the process into the left branch of the portal vein. Portal venous thrombosis may occur later in life, either spontaneously or from infection in the portal bed, or in rare instances it may result from trauma. It is of extreme significance that the liver in this type of case is essentially normal early in the course of the disease, as cirrhosis is one of the late manifestations. The first indication that this serious disease entity exists is almost without exception the occurrence of massive hematemesis or melena. The finding of an enlarged spleen and the blood picture of hypersplenism, or congestive splenomegaly, is frequently corroborative evidence of this diagnosis. The life expectancy in this disease is much longer than in cirrhosis of the liver, but the indications for shunt surgery are as clear because repeated esophageal hemorrhages result in a state of chronic invalidism and a very high morbidity in many of these patients. Furthermore, because of an essentially normal liver, the risk of operation in this group of patients is relatively small, so that the operative mortality is low. In our series of 24 patients with this type of disease, 26 shunts were performed with one death, an operative mortality of 4 per cent. A cavernomatous vascular change around the portal vein in the gastrohepatic ligament is found in many of these cases which precludes the exposure of it in most of them so that the end-to-side splenorenal shunt with splenectomy is the procedure that is recommended in this group. The operation of splenectomy alone is to be condemned seriously because, following such a procedure without the construction of a shunt, a splenorenal shunt cannot be performed at a later date because the splen vein becomes thrombosed and no longer u lizable. In addition, because of the cavern matous change in the gastrohepatic ligame it is impossible to construct a satisfacto direct portacaval shunt. It cannot be emph sized too strongly, therefore, *that any surge who does a splenectomy on a patient with extrahepatic portal bed block should not pe form this procedure unless he is capable the same time of constructing an end- side splenorenal anastomosis.*

LIVER FUNCTION TESTS

A thorough evaluation of the liver fun tions should be performed in all patients wi bleeding esophageal varices before subje ing them to shunt surgery, because the oper tive mortality is much higher in the patie with severe liver disease. Many liver functi tests have been devised. They fall into categories as described by Himsworth:[18] (tests of excretory function; (2) tests of t ability of the liver to synthesize; (3) empi cal tests of liver damage.

From the practical viewpoint the followi have been found to be most valuable estimating the liver function and the patien ability to withstand major operative pro dure such as a portacaval shunt operati The quantitative van den Bergh test and t bromsulphalein dye retention test are us routinely to check excretory function. T serum albumin level, the response of the p thrombin time, if elevated, to vitamin therapy, and the presence of ascites a whether or not it responds to medical th apy are used to test the liver's ability to sy thesize proteins. The cephalin flocculati test has been the most useful of the empiri tests to determine the degree of liver dama The alkaline phosphatase and the thym turbidity have been used also but are of l practical value. In addition to these tests, cases where the degree of liver damage m still be in doubt, a needle biopsy of the li may be done prior to surgery to determi more accurately the cytology of the liver c and the stage of the cirrhosis. An acute pr ess may be detected by this method which sufficient indication to delay shunt surg while further medical treatment is carr out.

An analysis of these liver function tests

TABLE 13. CORRELATION OF LIVER FUNCTION TESTS WITH POSTOPERATIVE DEATHS IN 75 OPERATIONS FOR BLEEDING ESOPHAGEAL VARICES
Massachusetts General Hospital, 1945–1951 (March)

TEST		NUMBER OF SURVIVALS	NUMBER OF DEATHS	MORTALITY RATE
m albumin	Less than 3 Gm. %	1	5	83%
	More than 3 Gm. %	57	6	9%
tes	Failed to respond to medical treatment	5	4	44%
	Disappeared on medical treatment	5	2	28%
	None	54	5	8%
hrombin time	More than 4 seconds	25	9	27%
above normal)	Less than 4 seconds	37	2	5%
halin flocculation	3+ to 4+	25	11	31%
	1+ to 2+	39	0	0
msulphalein	More than 10%	39	9	19%
ention 5 mg./kilo	Less than 10%	22	0	0
den Bergh	More than 1.0	30	6	17%
ubin mg./100 cc.	Less than 1.0	32	4	11%

tion to the operative mortality following operations on 68 patients for bleeding phageal varices reveals very interesting informative data (Table 13). Not all of surgical procedures were shunt opera- s, since some of the patients were con- ered too serious a risk to put them through h a long operative procedure. They are uded, however, in the following statistics completeness of the analysis of this group patients with severe liver disease under- ng major surgery.

rom the data obtained it is to be noted the finding of a serum albumin level ow 3 Gm. per 100 cc. seems to be of reme significance, since in 6 operations patients with this low albumin level 5 %) died postoperatively from hemor- ge or liver failure, whereas in 63 opera- s when the albumin level was above 3 . per 100 cc., only 6 patients died, an rative mortality of 9 per cent.

he presence of ascites, especially if it s to respond to medical therapy, is also wn to be of extreme prognostic impor- ce since 4 (44%) of the 9 patients with finding died as the result of surgery. ere were 7 additional cases in whom the ites disappeared on preoperative medical rapy and of these 2 (28%) died, demon- ting a lower but nevertheless a high mor- ty rate. The absence of ascites, on the er hand, seems to indicate that the patient is a safer risk, since in 59 patients only 5 died in this group—a mortality rate of 8 per cent.

A prolonged prothrombin time also was found to indicate serious risk patients when it failed to respond to adequate preoperative vitamin K therapy, because in 34 patients in whom the prothrombin time remained 4 seconds or more greater than normal, there were 9 deaths, or a mortality rate of 27 per cent, whereas in 39 patients in whom the response was more satisfactory with the prothrombin time reducing to within 4 seconds or less of normal, there were only 2 deaths, or a mortality rate of 5 per cent.

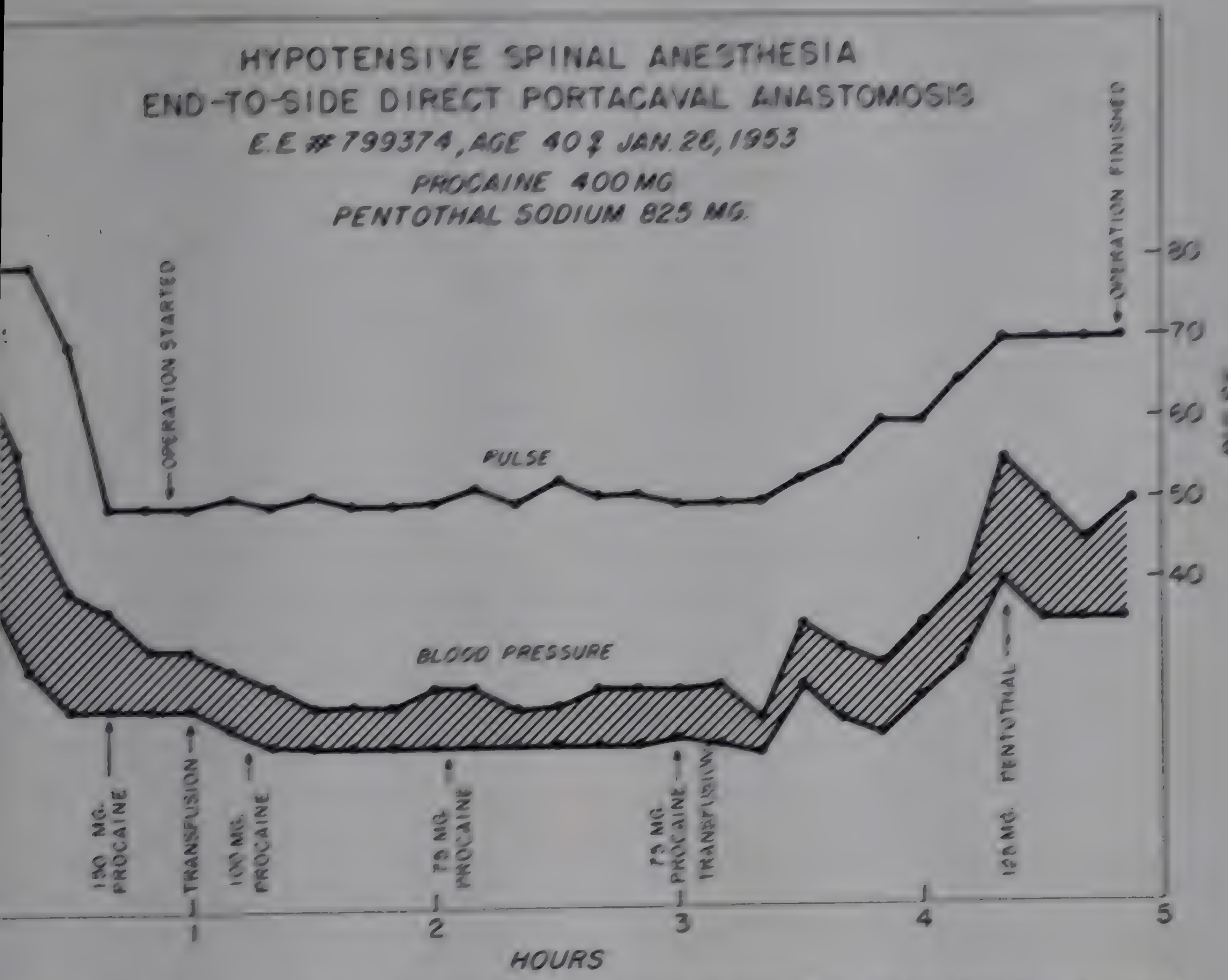
The results of the cephalin flocculation test indicate that it is of great prognostic value since when severe liver disease is demonstrated with a 3+ or 4+ flocculation, the mortality rate was extremely high and, in fact, all the 11 patients or 100 per cent of those who died, fell into this group. There were 36 patients with this degree of liver damage, and 11 (31%) died postoperatively, whereas in 39 patients with a 1+ or 2+ cephalin flocculation there were no postoperative deaths. These observations thus demonstrate that slight liver damage as shown by this test indicates that the patient is a fair to good operative risk, whereas with the more pronounced disease he is a serious surgical risk.

The bromsulphalein retention test, when it was less than 10 per cent after 45 minutes following the injection of 5 mg. per Kg. was of prognostic value, since in 22 instances falling into this group there were no deaths. Of 48 patients in whom the value was above this level, indicating more severe liver disease, 9 (19%) died postoperatively. It is to be noted, however, that in a number of patients with a very high retention, in some instances over 50 per cent, the convalescence following shunt surgery was remarkably uneventful. From these observations, however, it would appear to indicate that those patients with a normal dye retention are good surgical risks, whereas those with abnormal retention are not such good risks. The serum bilirubin level is an indication of the excretory function of the liver, and this was studied by obtaining quantitative van den Bergh determinations of the blood serum. In 36 instances when the bilirubin level was below 1 mg. per 100 cc., there were 4 postoperative deaths, or a mortality rate of 11 per cent. In 36 others, with the level above this figure in almost an equal number, there were 6 deaths, or a mortality of 17 per cent.

From these observations (Table 13) it would appear that the following liver-function tests indicate that a patient is a serious operative risk for shunt surgery in the order of their importance: (1) a serum albumin level below 3 Gm. per 100 cc.; (2) ascites which fails to respond to medical therapy; (3) a 3+ or 4+ cephalin flocculation; (4) a prothrombin time which remains prolonged more than 4 seconds above normal after adequate vitamin K therapy; (5) an elevated serum bilirubin; and (6) a bromsulphalein retention test showing more than 10 per cent dye retention after 45 minutes. Conversely, from the data obtained from these patients, it can be stated that the following values in these liver-function tests indicate that a patient may be a good operative risk in the following order of their importance: (1) a 1+ to 2+ cephalin flocculation test; (2) a bromsulphalein retention below 10 per cent after one half hour; (3) a prothrombin time within 4 seconds of normal; (4) a plasma albumin level greater than 3 Gm. per 100 cc.; (5) the absence of ascites; and (6) a serum bilirubin level below 1 mg. per 100 cc. Finally, it should be emphasized that the criteria of operability should not rest on one
test alone, but a careful evaluatio
patient should be made after obtai
results of these tests. The most seri
patient will be a jaundiced one with
albumin below 3 Gm. per cent per
with ascites that fails to respond to
therapy, with a 3+ or 4+ cephalin
tion, and a prothrombin time that
respond to therapy.

PREOPERATIVE, OPERATIVE
POSTOPERATIVE TREATM

The preoperative preparation of
for the construction of a portacaval
of extreme importance in order that
withstand these major surgical pr
The patients with an extrahepatic p
block require less preparation, as
since they have essentially normal li
in most instances have essentially
blood chemical determinations. A
they are anemic, so several transfus
be necessary to bring their hemoglo
up to at least 12 Gm., because the
procedure should not be perform
such a hemoglobin concentration is
The patients with an intrahepatic b
ondary to cirrhosis of the liver, on
hand, may be extremely difficult
pare for a shunt procedure. If
present it is essential to clear this by
measures, consisting of a high-pr
carbohydrate diet and the use of
When a low serum albumin level
respond to this therapy, the intrave
ministration of human albumin is
When the prothrombin time is p
vitamin K is given by mouth and
cularly in an attempt to restore it t
nearly normal level. As in the pati
the extrahepatic block, repeated blo
fusions are used to restore the he
to a normal level and at the sam
improve the level of the serum alb
some patients who come into the
with massive bleeding, the emergen
thoracic transesophageal suture of
phageal varices may be necessary
permit sufficient time for adequate
tive preparation. In most instance
tient can be prepared for an elect
caval shunt within 4 to 6 weeks



. 79. Reproduction of an anesthesia chart on a patient who had a direct portacaval
performed under hypotensive spinal anesthesia. Note the sustained low pulse rate
blood pressure. The anesthetic agents consisted of 2 intravenous injections of
ng. and 125 mg., each of Pentothal Sodium; and 4 intraspinal subarachnoid injec-
of procaine, each of 150 mg., 100 mg., 75 mg. and 75 mg., totaling 400 mg.
were given through a fine catheter inserted into the spinal subarachnoid space. The
tive procedure required approximately 4 hours, and instead of the usual 4 to 8
transfusions needed for similar operations under normotensive blood pressure,
1 was required in this case because so little blood was lost. No serious effects to
eart, the brain, the liver or the kidneys from this prolonged state of hypotension
een noted in our cases.

l patient has required as long as
nonths. This careful preoperative
on, without question, will reduce the
mortality for constructing a porta-
nt, and its importance cannot be
asized.

IVE TECHNIC OF CONSTRUCTING
A PORTACAVAL SHUNT

e decision has been made to oper-
a patient with a history of bleeding
l varices in order to construct some
ortacaval shunt, the choice of the
is of utmost importance. It is be-
t the type of anesthesia plays a very important role in the mortality rate of these long, major surgical procedures, especially in patients with diseased livers. Ether anesthesia was used routinely early in the course of our experience, and in many instances a hemorrhagic diathesis developed, which, in some cases, was uncontrollable, during the operative procedure, and from which most of our early deaths occurred. A study of the effect of ether during these procedures revealed that it has a toxic effect on the liver and interfered with the blood-clotting mechanism and, for that reason, was abandoned. Cyclopropane anesthesia was chosen next because it seemed to have a less damaging

effect on the sick liver, with the result that deaths from operative hemorrhage became less common. This was aided also, in part, by the use during the operation of fresh-blood transfusions as recommended by Souttar[41] that supply a thrombin accelerator factor which frequently is reduced in these patients with severe liver disease and also is absent in most blood-bank transfusions. Despite these advances it was still necessary to utilize from 5 to 10 blood transfusions during each operative procedure. During the past 4 years hypotensive spinal anesthesia, given according to Gillies' technic,[15, 16] has been utilized in most of the patients. There have been no complications from this method of anesthesia, and no deaths from hemorrhage. Furthermore, there has been a great saving of transfusions because in most instances only 1 or 2 transfusions, and at the most 3, are all that have been necessary, since the reduction in the systemic arterial blood pressure reduces the blood loss during the operative procedure to a great extent. In addition, it is noteworthy that there were no untoward effects on the liver, the kidneys, the brain or the heart with this type of anesthesia. In our hands at the present time it is the anesthesia of choice, but requires, of necessity, an anesthesiologist well trained in the technic (Fig. 79).

Splenorenal Anastomosis. For this procedure the patient is placed on his right side and tipped back to about 45° with the horizontal (Fig. 76). A long oblique incision is used, extending from just above the umbilicus to the angle of the tenth rib. The incision is carried into the abdominal and the pleural cavities, removing the tenth rib subperiosteally; the diaphragm is partially severed to expose the spleen. The spleen is removed, carefully isolating and ligating all the blood vessels that are encountered. The splenic artery and the splenic vein are ligated separately, taking care to preserve as much of the splenic vein as is possible. A pressure determination is made in this vessel to compare with one taken after completing the shunt. Then the left renal vein and artery are exposed in the retroperitoneal area without freeing up the kidney. The length of splenic vein that will be necessary to construct an end-to-side splenorenal shunt is determined, and at this point it is freed up from the pancreas. A number of small pancreati branches must be isolated and l carefully. The renal artery is clamp fully with a small bulldog clamp. T vein is isolated between two occludin and with a bulldog clamp on the part of the splenic vein, an end-to-s tomosis is constructed between the the splenic vein and the side of the re after excising an ellipse of the wa latter. A running, everting type of suture of No. 5-0 silk is used so intima-to-intima approximation is This is a very important step in th dure to prevent thrombosis from at the site of the suture. After compl anastomosis, the occluding clamps moved, and the splenic vein pressu corded, since in this way it can be de how effective the anastomosis is in the portal blood into the systemic ve tem. Then the abdominal, thoracic phragmatic incisions are closed.

Portacaval Anastomosis. For this shunt the patient is placed on his at a 90° angle to the operating table and 78). A long incision is made, from the angle of the tenth rib to j the umbilicus, opening the thoracic abdominal cavities. The tenth rib is subperiosteally. The diaphragm is that it is possible to displace the live into the pleural cavity. This gives lent exposure of the subhepatic ar the inferior vena cava and the portal The former is exposed readily. T vein in many cases, provided that men of Winslow is opened and free sions, is also readily found in the margin of the gastrohepatic ligam rule, the common bile duct and th artery are visualized in order to pro They lie anterior and to the left an are far enough away from the p with the patient in this position t damage to them unless one runs cavernomatous change in the gast ligament, which makes exposure of structures exceedingly difficult. Th mosis is constructed by isolating a the anterior wall of the vena cava shaped clamp and excising an el The portal vein is interrupted, firs ing it with a transfixion suture

distal to this ligature. Bleeding is
with a tourniquet type of clamp.
-side anastomosis is constructed
hat used for the splenorenal shunt.
venous pressure is taken after the
completed and is compared with
re previous to the shunt, again to
the effectiveness of the anastomo-
rule this is a more effective shunt
educing the portal pressure is con-
fact, care should be taken not to
large an opening, since there should
resistance at the site of anastomo-
event the portal venous pressure
pping too near to the level of the
venous pressure, since this would
lood flow through the anastomosis,
voring thrombosis of it. The tho-
abdominal and the diaphragmatic
are closed carefully, usually with
d nonabsorbable sutures.

POSTOPERATIVE CARE

stoperative care in these patients is
e importance. It consists of restor-
rculating blood volume to normal
transfusions, maintaining fluid and
e balance with intravenous glucose
rimarily and good oxygenation by
oxygen at 6 to 7 liters a minute
small tube inserted into the naso-
hrough one of the nares. In the pa-
h cirrhosis, Demerol is used as a
n preference to morphine. The con-
e is uncomplicated in the majority
ts, and they usually can be dis-
rom the hospital within 2 weeks
time of operation. The patients with
tic blocks are soon restored to nor-
many of the ones with intrahepatic
quire a long period of convalescence
their discharge from the hospital
f the underlying liver disease.

RY OF RESULTS OBTAINED H PORTACAVAL SHUNT RATIONS FOR BLEEDING HAGEAL VARICES AT THE SSACHUSETTS GENERAL HOSPITAL (1945–1952)

nstruction of a splenorenal or a
tal vein to inferior vena cava anas-
o bypass the portal blood in patients with an intrahepatic or an extrahepatic portal bed block, is believed to be the most satisfactory method of controlling hemorrhage from esophageal varices, as the following analysis of our cases reveals. *It is to be emphasized that every patient who has bled from esophageal varices should be considered a candidate for some type of portacaval shunt, rather than any other form of treatment. It is important to understand that the construction of a portacaval shunt should not be done for the relief of chronic ascites without portal hypertension.* In the patients that have been followed, there has been little if any improvement in the liver-function tests following the construction of a shunt, so that the operation should not be performed with the expectation that the liver function will necessarily improve. In general it can be stated that for the most part there are 3 groups of patients with bleeding esophageal varices who are the most suitable for this type of surgery: (1) those with portal cirrhosis without ascites; (2) those with portal cirrhosis and ascites that responds to medical treatment; and (3) those with an extrahepatic type of portal bed block.

The construction of some type of portacaval shunt has been the method of choice in the treatment of bleeding esophageal varices at the Massachusetts General Hospital since 1945. Ninety patients have had either a splenorenal or a direct portacaval shunt performed up to January 1, 1953 (Table 14). The results obtained in this group of patients have been extremely encouraging, as the following analysis reveals in these cases followed from 1 to 7 years. There were 24 (27%) who had an extrahepatic portal bed block, and 66 (73%) with an intrahepatic block secondary to portal cirrhosis of the liver. There were 30 females (33%) and 60 males (67%); 9 females (27%) had an extrahepatic block,

TABLE 14. TYPES OF PORTACAVAL SHUNTS
Massachusetts General Hospital,
1945–1952, Inclusive

Splenorenal	68	72%
Direct portacaval	22	23%
Others	4	5%
Totals	94	100%

and 15 (63%) were males, while in the patients with cirrhosis of the liver there were 21 (32%) females and 45 (68%) males. The youngest patient was 6 years of age, and the oldest 70 years. Bleeding esophageal varices were most common in mid-life, since 64 (70%) of them were between 30 and 60 years of age.

A total of 94 shunts was performed in these 90 patients, since in 4 patients—3 with splenorenal anastomoses and 1 with an inferior mesenteric vein to left ovarian vein who had secondary hemorrhages—direct portacaval anastomoses were performed at later dates. There were 68 end-to-side splenorenal shunts with splenectomy (72%); 22 (23%) had direct anastomoses between the portal vein and the inferior vena cava; 18 (86%) of these were end-to-side, and 4 (14%) were side-to-side; 4 other patients (5%) had other types of shunts, including anastomoses between the superior mesenteric vein and the inferior vena cava—the inferior mesenteric vein and the left ovarian vein in one case and in another to the left adrenal vein (Table 14). This latter group of 4 shunts is what might be termed "makeshift" shunts; they were performed because it was impossible to construct a splenorenal shunt due to a previous splenectomy in each case, and a cavernomatous change in the gastrohepatic ligament around the portal vein which made it impossible to isolate this blood vessel. The latter 2 types of shunts are no longer attempted in our clinic because of the poor results obtained in these patients. In one case a satisfactory result has been obtained with the anastomosis between the superior mesenteric vein and the inferior vena cava, but this type is not considered as good as a splenorenal or a direct portacaval shunt. In the 24 patients with the extrahepatic portal bed block, 26 shunts were performed: 20 (76%) were end-to-side splenorenal anastomoses; 3 (12%) had direct portacaval anastomoses; and 3 (12%) had the other types. The greater incidence of the splenorenal shunts in this group of patients was due to the cavernomatous transformation of the gastrohepatic ligament.

There were 66 cases of cirrhosis of the liver with an intrahepatic portal bed block in whom 69 shunts were performed: 49 (71%) were end-to-side splenorenal an
moses; 19 (27%) were direct portac
and in 1 a superior mesenteric vein t
ferior vena cava shunt was performed. V
direct portacaval shunts were constructe
this group because the portal vein is exp
more readily in these patients, and in s
cases the spleen is small, indicating that
splenic vein will not be large enough to m
a satisfactory shunt. An attempt is b
made to determine, if possible, which typ
shunt is superior from the viewpoint of
venting further esophageal bleeding, and
what effect each procedure might have
liver function in addition to their respe
mortality rates. At the present time
believed that the operative risk is less in
tients who have the splenorenal shunt
formed, since most of our deaths from
failure and hemorrhage have followed
direct portacaval anastomoses. Furtherm
late complications seem to be more p
lent in the same group. However, to cou
balance this, there is no question but tha
direct portacaval shunts do reduce the
tal hypertension more effectively and t
fore give better protection against fu
esophageal bleeding. From the surgical
point, it is also an easier shunt to cons
provided that the cavernomatous chan
the gastrohepatic ligament is not en
tered. Further studies are needed to
mine, if possible, if there is any differen
the long-term survival of these pat

TABLE 15. SURGICAL MORTALITY RATE
SPLENORENAL AND PORTACAVAL SHUNT O
TIONS PERFORMED AT THE MASSACHUSE
GENERAL HOSPITAL, 1945–1952, INCLU

YEAR	NUMBER OF OPERATIONS	NUMBER OF OPERATIVE DEATHS	MOR R
1945	3	1	3
1946	6	3	5
1947	6	1	1
1948	20	2	1
1949	7	3	4
1950	19	1	
1951	16	1	
1952	17	1	
1953	20	1	
Totals	114	14	

lly those with severely damaged liv-
 date it has been a disappointment
ere has been little, if any, improve-
 the liver functions, as measured by
ious tests following either the spleno-
r the direct portacaval anastomoses,
hough no further bleeding episodes
ccurred. An analysis of this group of
 who have undergone splenorenal or
val shunts reveals that 78 (86%) of
tients survived the operations, giving
rative mortality rate of 14 per cent.
 the year 1953, 20 additional patients
unts performed with 1 death, making
of 114 cases with 14 deaths, or an op-
 mortality of 12 per cent (Table 15).
 extreme significance that the majority
postoperative deaths, as might be ex-
 occurred in the early years, while the
 technics of preoperative preparation,
esia and operative procedures were
leveloped. It is to be noted that during
t 4 years there have been no deaths
mmediate postoperative hemorrhage,
ly 4 deaths in the last 72 shunts per-
l, or an operative mortality rate of 5
nt. Three of the deaths resulted from
ilure, 2 following a direct portacaval
mosis and 1 a splenorenal. The fourth
 died from pancreatic necrosis and
following a splenorenal shunt.

 reduction in the mortality rate, it is
d, is the result of the more careful
ation of the patients with sick livers;
mination of the hemorrhagic diathesis
ing during the operative procedure,
 utilizing fresh blood transfusions dur-
 operation, and also the use of cyclo-
e anesthesia instead of ether; and,
 the use of hypotensive spinal anesthesia given according to Gillies'[15, 16] technic, which eliminates almost completely any danger of severe hemorrhage during the operation. Finally, the perfection of the technic for this type of surgery, without question, has been a factor in the lower mortality rate in recent years. The immediate postoperative mortality, as might be expected, is much greater in the cirrhotic group than those with the extrahepatic block, since the patients in the former group have severely damaged livers as a rule, and the latter essentially normal ones. There were 69 shunts in the intrahepatic, or cirrhotic group, with 6 deaths from early postoperative hemorrhage in the operative field—4 from liver failure and 2 from sepsis—a total of 12 deaths or an operative mortality of 17.4 per cent; whereas there were 25 shunts performed in the extrahepatic group, but only 1 death from postoperative hemorrhage, an operative mortality rate of 4 per cent.

The follow-up studies in this group of patients have been of extreme interest, especially from the viewpoint of recurrent bleeding (Table 16). In 60 survival patients who had splenorenal shunts, it was found that 3 (5%) of them developed minor bleeding not requiring hospitalization. In 5 patients (8%) major bleeding developed. In 4 of these, secondary direct portacaval anastomoses have been performed with relief of bleeding in 2 of these patients. There has been 1 death in this group from massive bleeding from esophageal varices, an incidence of 1.7 per cent. In 18 patients with direct portacaval anastomoses, there were no incidences of minor bleeding. There were 2 patients who had major bleeding, and in 1 of these it had been necessary to do a throm-

TABLE 16. SUMMARY OF ESOPHAGEAL BLEEDING FOLLOWING 78 SURVIVAL SHUNT OPERATIONS
Massachusetts General Hospital, 1945–1952, Inclusive

TYPE OF SHUNT	NO. OF SHUNTS	POSTSHUNT BLEEDING		
		Minor	*Major*	*Deaths from Bleeding*
Splenorenal	60 (80%)	3 (5%)	5* (8%)	1 (1.7%)
Portacaval	18 (20%)	0	2** (11%)	0
Totals	78 (100%)	3 (4%)	7 (9%)	1 (1.3%)

of these patients had secondary portacaval shunts with relief of bleeding in 2.
of these patients had a thrombosed portal vein.

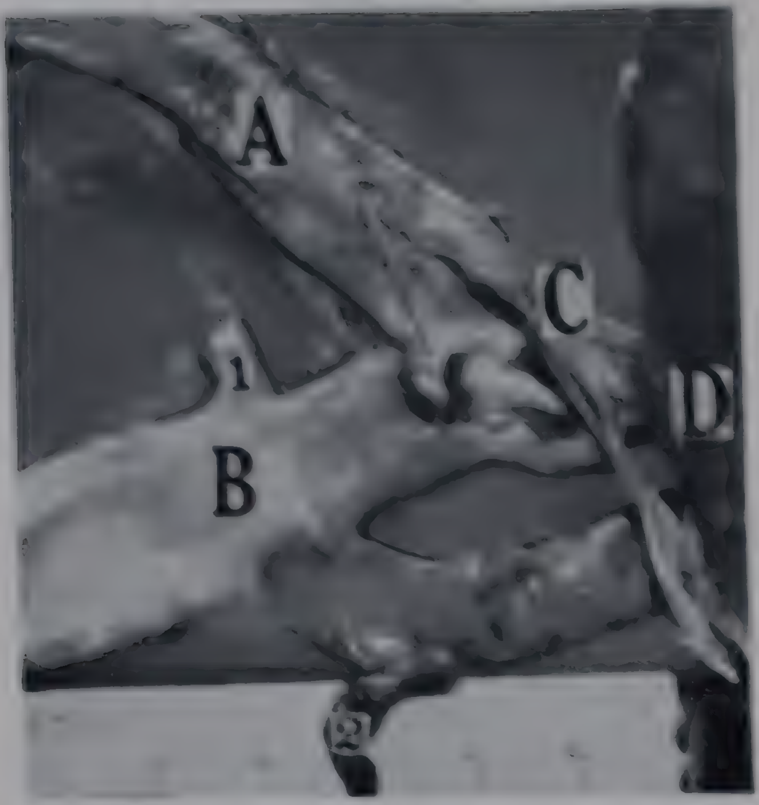


FIG. 80. End-to-side splenoren
tomosis removed at autopsy 8 m
after it was constructed. The pati
man) had bleeding esophageal v
secondary to portal cirrhosis with
trahepatic portal bed block. No bl
occurred after the shunt was perfo
He died of acute alcoholism. (A
splenic vein. (B) A bifid renal vein
ing (1) the adrenal vein and (2
spermatic vein. (C) The site of the
tomosis between the end of the s
vein and the side of the upper bra
the renal vein. A portion of the a
walls of these veins has been cut a
show the intima at the anastomosis
how smooth it is, with no evide
thrombosis and none of the silk s
used to construct it are visible. It a
appears like a natural venovenous
tion instead of a surgically cons
one. (D) The edge of the kidney
hilum.

bectomy of the portal vein in order to reestablish the lumen of it because of portal vein thrombosis, in order to construct a satisfactory anastomosis. In this patient, it is feared that secondary thrombosis occurred, since the intima of the vein was very ragged after removing the clot. There have been no deaths from bleeding following any of the direct portacaval shunts. In summary, then, it can be stated, that in 77 patients who survived the shunt procedures, there have been 3 cases of minor bleeding, or an incidence of 4 per cent; 7 cases of major bleeding, or 9 per cent; and 1 death, or an incidence of 1.3 per cent.

A further analysis (Table 17) reveals that
in 23 patients with the extrahepat
bed block who survived the constr
a splenorenal or a portacaval sh
has been only 1 death in the follo
riod from 1945 to 1952. This pat
4 years after the shunt was perform
a cerebral hemorrhage, a condition
to the portal hypertension. In the
patients with an intrahepatic po
block secondary to cirrhosis of t
there were 54 patients who surv
construction of a shunt, and in this
(13%) have died from various c
from liver failure at 8, 20, 23

TABLE 17. LATE DEATHS FOLLOWING SPLENORENAL AND PORTACAVAL SHUNTS
77 SURVIVAL PATIENTS
Massachusetts General Hospital, 1945–1952, Inclusive

TYPE OF BLOCK	NO. OF PATIENTS	NO. OF DEATHS	CAUSES OF DEATHS			
			Liver Failure	*Heart Failure*	*Cerebral Hemorrhage*	*E H*
Extrahepatic (Banti's disease)	23 (29%)	1 (4.3%)	0	0	1 (4 yrs.)	
Intrahepatic (cirrhosis)	54 (71%)	7 (13%)	4 (8, 20, 23, 43 mos.)	1 (5 mos.)	1 (19 mos.)	1
Totals	77 (100%)	8 (10.7%)	4	1	2	

TABLE 18. END-RESULTS OF PORTACAVAL SHUNTS IN 90 PATIENTS WITH BLEEDING ESOPHAGEAL VARICES
Massachusetts General Hospital, 1945–1952, Inclusive

PORTAL OCK	NO. OF PATIENTS	POST-OPERATIVE DEATHS*	LATE POSTSHUNT DEATHS**	TOTAL SURVIVALS	EXPECTED SUR-VIVAL RATE WITHOUT SHUNT
(Banti's d	24 (27%)	1 (4%)	1 (4.3%)	92%	70%
(cirrhosis	66 (73%)	12 (18%)	7 (13%)	71%	20%
	90 (100%)	13 (14%)	8 (10%)	77%	

*ve been only 4 postoperative deaths in the last 72 shunts performed, or a mortality rate of

*f these deaths were unrelated to the esophageal varices or cirrhosis of the liver.

pectively, after the shunts were
1 from heart failure 5 months
he shunt; another from cerebral
19 months after it was per-
additional patient has succumbed
ive esophageal hemorrhage 12
er a splenorenal shunt. The ma-
ese patients have had postmortem
ns, and the venovenous anasto-
found to be patent without evi-
rombosis (Fig. 80). In summary
there were 77 patients who sur-
onstruction of a splenorenal or a
acaval shunt: 8 of these patients
are dead; the remaining 69
still alive and, for the most part,
ealth for periods ranging from 1
after the shunts were constructed.
lts are a tremendous improve-
the expected mortality rate in a similar group of patients followed over a period of the same number of years, since Shull showed in our hospital that a mortality rate in patients with bleeding esophageal varices secondary to an extrahepatic portal bed block was between 10 to 30 per cent, and in patients with an intrahepatic block secondary to cirrhosis of the liver, the expected mortality rate ranged from 50 to 80 per cent for periods of 1 to 5 years (Table 18). In conclusion, it can be stated, from a study of these patients, that the construction of some type of portacaval shunt, either an end-to-side splenorenal anastomosis with splenectomy, or a direct anastomosis between the end of the portal vein and the side of the inferior vena cava, is an important advance in the treatment of this serious complication of portal cirrhosis and portal venous thrombosis.

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Chapter 9 HEPATIC COMA

Charles S. Davidson, M.D.

DEFINITION

Patients with severe liver disease may lapse into a comatose state which usually ends fatally and may continue for from a few days to several weeks. The term "liver coma" or "hepatic coma" is applied to this state of unconsciousness and usually is extended to include the early clinical manifestations preceding actual loss of consciousness. The early stages of the condition are described sometimes as "impending hepatic coma," but not all patients in whom coma appears to be impending progress to loss of consciousness. In this discussion the term "hepatic coma" will be used to refer to all alterations in the state of consciousness in patients with severe liver disease whether true coma exists or is only expected.

Other terms have been used to describe this peculiar change in the state of consciousness of patients with severe liver disease. Some of these are "cholemia," "liver failure" and "hepatargy." The first two of these terms imply conditions which need not exist in patients with hepatic coma, as will become evident in subsequent discussion, and the third has not acquired general acceptance. It was Leyden in 1866[36] who proposed the term cholemia for the comatose state in liver disease. He attributed the coma to retention of bile acids in the blood and pointed out its clinical resemblance to uremia. There is no evidence that the retention of bile acids is implicated in the pathogenesis of hepatic coma; therefore, the term cholemia, although frequently used, has become meaningless from the point of view of etiology and should be avoided. The term hepatic coma, in spite of the limitation that all patients may not be or even become comatose, is considered as the best and most widely accepted term to embrace all the clinical manifestations of
syndrome.

Hepatic coma is one of the most frequ
terminal episodes of patients with prim
liver disease. In cirrhosis of the liver P
and Ratnoff[49] found that 36 per cent of t
patients died in hepatic coma. It is the u
terminal event when viral hepatitis occas
ally ends fatally, and it is observed in pati
with Wilson's disease (hepatolenticular
generation), biliary cirrhosis and hemoc
matosis. The series of 60 patients studie
Adams and Foley[1] at the Boston City
pital consisted of 48 with Laennec's cirrh
of whom all but 7 were chronic alcoholic
with hemochromatosis, 4 with infect
hepatitis, 1 with biliary cirrhosis, 1 with
hepatitis, and 3 with acute or sub
atrophy of the liver. The preponderanc
alcoholics probably reflects the populati
the hospital where the study was made
cause of its frequency the hepatic com
pearing in patients with Laennec's cirr
has been best described and qualified a
the prototype of the remainder. There
to be little reason to discuss separatel
patic coma as it appears in the various
of liver disease because the clinical mani
tions and presumably the pathogenesis
disturbance are similar for all. The p
exception to this generalization is in the
acute forms of liver disease, particularly
atrophy in which mania, sometimes wi
lucinations, may be observed before the
of coma (Adams and Foley[1]).

CLINICAL MANIFESTATIO

W. Griffin[24] of Limerick was one
first physicians to call attention to con
terminal episode in liver disease.
scribed 4 cases in the same family.

on which follows suggests infectious
tis or possibly leptospirosis.

> oor woman requested me to visit her
> ter, Mary Barry, aged twenty years, who
> formed me had been three days ill, and
> ow speechless, and she believed dying. On
> ng the cabin in which she lived, I saw
> ake a faint expiration, which proved to
> r last, as she was quite dead when I
> ed the bed. Her skin was still warm, and
> sally tinged with a deep yellow colour.
> ountenance was hydropic, and the pupils
> d. On inquiring, I found the girl's ailment
> et in with langour and heaviness; on the
> d evening she was seized with sickness of
> ch, vomiting, and appearances of jaun-
> and next morning complained much of
> ead. She then looked so very ill, that her
> er began to get alarmed, and insisted on
> oing to the dispensary for advice; the
> girl shook her head despondingly, and
> he was too weak to walk there, but that
> ould go into the room and lie down on
> ed. These were the last words she uttered;
> the mother went in afterwards, there was
> pearance of stupor about her, from which
> ndeavoured to rouse her, but could get no
> —She was in profound coma!

erichs[21] in 1860 described many of the
festations of prolonged coma as a ter-
event:

> Cases have occurred to me in which individuals who for a long period of time have suffered from cirrhosis of the liver, have suddenly presented a series of morbid symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with a noisy delirium, from which they passed into deep coma, and in this state have died. In most cases slight jaundice made its appearance at the same time. . . .

This statement would be little changed today except for a more detailed description of the early stages and of fetor (discussed elsewhere).

ONSET AND DEVELOPMENT

The recognition of the early stages of hepatic coma is important because therapy and preventive measures may be taken then with the best hope of success. Table 19 shows a partial classification of the stages in the progress of this condition.

1. Onset. The onset of this neurologic disturbance in patients with severe liver disease is usually very gradual and may be almost imperceptible ("Prodrome," Table 19). Murphy et al.[42] noted a loss of affect and a defect in judgment in the early stages. A certain degree of euphoria (sometimes quite marked) is seen, although occasionally the patients may be depressed and apathetic.

TABLE 19. STAGES IN ONSET AND DEVELOPMENT OF HEPATIC COMA

	MENTAL STATE	TREMOR	E.E.G. CHANGES
ome (often y in retrospect)	Euphoria, occasionally depression Confusion, absent or difficult to detect Slight slowing of mentation Untidiness	Often present but slight	Usually absent
nding Coma	Confusion Usually euphoria Drowsiness Inappropriate behavior	Usually present and easily elicitable	Almost always present
r	Sleeps most of time but arousable Confusion, marked	Usually present if patient can cooperate	Almost always present
coma or Coma	Unconsciousness May respond to noxious stimuli or, when deep, may respond not at all	Usually absent (no muscle tone)	Often present

Patients at this stage are often untidy and exhibit inappropriate behavior. Sometimes sleep is upset, the patients being drowsy or even sleeping through long periods of the day but being wakeful and sometimes noisy and confused during the nights. Often many of these abnormalities may be absent or extremely difficult to detect in the early stages. Often hypnotics are prescribed because of the nocturnal wakefulness, but they should not be given unless absolutely necessary and then with great caution, because many of the sedatives are poorly tolerated and may play a part in the genesis of hepatic coma (for further discussion see p. 246).

2. Impending Hepatic Coma. The next stage, which is considerably more specific, has been called impending hepatic coma. Here there is clear-cut mental confusion characterized in its early stages merely by slowness of response but soon progressing to confusion with respect to time, place or person. The detailed and accurate clinical observations of Adams and Foley[1] have helped immeasurably to clarify and characterize the early stages of hepatic coma. A characteristic tremor is almost invariably observed. Although irregular involuntary movements have been noted by a number of authors for many years, it was Adams and Foley[1] who first clearly described the tremor. Their description follows:

> Concomitant with the change in the state of consciousness there appeared in the majority of cases a characteristic type of involuntary movement. This was most consistently and most effectively demonstrated by having the patient hold his arms and hands outstretched with the fingers spread apart. Depending upon the severity of the process, as this posture was maintained there appeared at irregular intervals of a fraction of a second to seven seconds, a series of movements consisting usually of lateral deviations of the fingers, flexion-extension of the fingers at the metacarpophalangeal joint, and flexion-extension of the wrist. The movements are rapid and arrhythmic—at one phase, for example, flexion, when the arms were outstretched in a pronated position, was always more rapid than the other. They tended to occur in bursts, at a rate of one or two per second. There were, however, intervals during which none of these movements were seen. In the more severe cases, as the arms were outstretched, there was the flexion-extension mov ment at the elbow and at the shoulder.

They also observed these same rhythmic movements in the legs when the recumbe patient was asked to dorsiflex his foot, in t face upon strong closure of the eyelids ar as well upon retraction of the corners of t mouth, pursing the lips, or protruding t tongue.

Although frequent, the "flapping tremo is not observed in every patient with i pending coma. When deep coma ensues, t tremor usually disappears because the p tient is unable to sustain a posture to bri out the tremor. When recovery occurs t tremor usually disappears but may contin for days or occasionally even months. As its specificity, an identical or very simil tremor has been seen by Adams and Fole in 2 uremic patients, 3 polycythemic patier with heart failure and mental confusion, a in 2 cases with hypokalemic stupors. Simi observations have been made by the auth Thus, the tremor is not absolutely speci nor is it seen in every patient with imper ing coma. Nevertheless, it is such a chara teristic phenomenon in impending hepa coma that its presence in a patient w severe liver disease should awaken the phy cian at once to the probability that co will ensue.

The third characteristic of impending patic coma is an abnormality in the elect encephalogram first described by Fol Watson and Adams[19] and consisting "paroxysms of bilaterally synchronous, sy metrical, high voltage, slow waves in delta range of 1½ to 3 per second" . "interspersed with or" . . . "superimpo on relatively normal (alpha) waves."[1] In early stages these "slow rollers" often oc in bursts and appear first in the frontal gions, later to spread laterally and po riorly until the entire record is of s activity. Some patients failed to show th changes during any stage of the progres hepatic coma. However, Adams and Fo found that of 25 patients 22 had typ waves at some phase. These electro-ence alographic abnormalities are not spec since they may be seen occasionally in o neurologic disturbances, particularly t of a metabolic nature.

though mental confusion, the flapping or, and the electro-encephalographic ges may not all be present and are not idually necessarily specific for hepatic a, the combination of the three makes liagnosis of impending hepatic coma al- inevitable in a patient with severe liver ase, and the occurrence of any one or in such a patient should lead the phy- n strongly to suspect that impending tic coma is present, so that he can ify his treatment accordingly. Patients impending hepatic coma may remain in stage for from a few hours to many days ven weeks with minor or major fluctua- s in the state of consciousness during this . Some may recover from this state en- y, either spontaneously or after preven- and therapeutic measures have been ertaken. For others, particularly those active hepatic disease, no measure ns to alter the inevitable progress to or, coma, and a fatal termination.

. **Coma.** Characteristically, as time goes he confusion deepens, the patient sleeps longer periods of time, becomes at first cult and then impossible to arouse; that oma has supervened. The coma may vary n a state in which reflexes are present the patients respond to painful stimuli movements or a cry or moan to deep na with areflexia, absent corneal reflexes failure to respond to any stimulus. Most ents during this stage of coma appear to casual observer as though sleeping peace- y. Vital signs, such as temperature, pulse respirations may not be abnormal. At es, particularly when complicating infec- s ensue, fever may occur, together with nycardia and tachypnea. Respirations are netimes unaccountably long, slow and p.

Rigidity of the limbs is seen frequently varies considerably and in the patient n time to time. When deep coma has ued, little or no rigidity is evident; but ing the earlier stages there may be re- ance to passive movement of the limbs, only occasionally is true cogwheel rigid- present. Convulsions may be seen. ams and Foley[1] report that about a third their patients at one time or another had onvulsion, usually near the terminal stage of the coma. Others have reported a much lower incidence. The deep tendon reflexes also vary considerably in their response. Sometimes hyperreflexia is present. At other times absence of reflexes, sometimes on one side and sometimes bilaterally, will be seen. Adams and Foley[1] report ankle clonus in about 20 per cent of their patients and extensor plantar responses in 75 per cent. Walshe[73] found ankle clonus in most of his patients, often before the plantar response became abnormal. Indeed, if these patients are watched carefully some reflex changes and plantar extension, sometimes unilateral and other times bilateral, will be seen in most patients. Grasping and sucking reflexes are seen sometimes.

Death of patients in hepatic coma may occur occasionally with no apparent precipitating cause other than prolonged coma. Most patients have a terminal episode of bronchopneumonia, and some of massive gastro-intestinal bleeding.

COURSE AND PROGNOSIS

The duration of hepatic coma may be from a few hours to 2 weeks or occasionally even longer. A week of deep coma is by no means unusual. Counting the onset from the first appearance of mental confusion or other signs of impending coma, the duration may be prolonged to weeks or months. Highly characteristic of hepatic coma is its tendency to fluctuate, particularly in the early stages. Thus, patients may be alert and with a barely detectable flapping tremor in the morning hours only to be confused and even stuporous with a severe tremor in the evening or night. Even deep coma usually will fluctuate in its depth from time to time. Sometimes patients who have been in deep coma for a few hours or even a few days may wake, and all signs of hepatic coma may disappear. Generally speaking, the deeper the coma and the longer it has persisted the less likelihood there is for a favorable response. Hence, the longer the coma, the poorer the prognosis. The fluctuations in depth of coma and the spontaneous remissions make the study of the disease and especially assessment of the efficacy of therapy extremely difficult and cast some doubt on many of the therapeutic measures which have been proposed (see section on Treatment).

PRECIPITATING FACTORS

Murphy et al.[42] in a study of 40 patients with hepatic coma at the Boston City Hospital found that in half of them the coma appeared to arise spontaneously; that is, no precipitating factor could be found. The other 20 patients had what these authors described as complicated hepatic coma as differentiated from the spontaneous or uncomplicated cases. Seventeen of these patients had severe infection (7 with pneumonia, 4 with tuberculosis, 4 with peritonitis, and 2 with bacterial endocarditis). Two patients lapsed into coma after bleeding from esophageal varices, and one patient had a hepatoma complicating Laennec's cirrhosis. Cerebral metastases from this tumor may have contributed to the mental symptoms in this case. Coma may also appear after bleeding from gastritis or duodenal ulcer or may follow abdominal paracentesis within a few hours or a day or two. The relationship of these other diseases and complications to the pathogenesis and the onset of coma in patients with severe liver disease will be discussed further in the section on Pathogenesis. Usually the onset and the course of hepatic coma in the complicated cases are more rapid than in that arising apparently spontaneously. However, the prognosis is considerably better in the former, presumably because the complicating factors—many of them—are amenable to therapy. The use of antibiotics in the treatment of infection and transfusions and other measures in acute gastro-intestinal bleeding favorably influence the prognosis in the complicated cases. Sedatives, as mentioned above, may appear to play a part in inducing hepatic coma or may prolong the course and make more likely a fatal termination.

LABORATORY FINDINGS

The usual laboratory tests are of little help, either in making a diagnosis of the hepatic coma or in deciding upon prognosis except in establishing the presence and the severity of the liver disease and in assessing the status of precipitating factors and complications such as pneumonia and gastro-intestinal bleeding. Anemia is a comr occurrence in liver disease, but it does bear any apparent specific relation to onset of the coma except when acute gas intestinal bleeding is a precipitating fac That is, the chronic macrocytic anemia liver disease is as common in patients hepatic coma as those without.

In a similar manner the white blood count is specifically related to the coma state only as an evidence of infection example, bronchopneumonia) or of the ticularly active form of cirrhosis of a holics emphasized by Phillips and Da son[51] in which leukocytosis, jaundice terminal coma are the rule. Murphy et found a distinct tendency for the white co to rise in many of the patients they stu with hepatic coma. White counts of 20 were not unusual in their series, the leu cytosis being usually a sign of terminal fection.

The blood nonprotein nitrogen concen tion may remain perfectly normal thro out a period of hepatic coma even whe ends fatally, although usually a gradual is noted which is more abrupt termin Several mechanisms may account for In the first place, oliguria, as will be cussed later, is a common accompani of hepatic coma. Second, acute ga intestinal hemorrhage may be a fa Third, an insufficient caloric intake cause protein to be burned for energy. mic levels of azotemia are observed commonly. Mild acidosis is a commo companiment of hepatic coma, alth patients may be carried for days in coma without a significant reduction in carbon dioxide combining power or pH. Hypoglycemia is not characterist hepatic coma, nor is hyperglycemia often seen than it is in liver disease normal mental state. Severe hypogly with hypoglycemic coma may be seen sionally in patients with severe liver di usually those with fibrosis of the pan as well (especially hemochromatosis). is an unusual occurrence, and the com state is not true hepatic coma but res rapidly to the administration of g solutions.

As a general statement, it may be sai

er-function tests in hepatic coma, al-
greatly disturbed and indicating the
y of the liver disease, appear to be
ted to the onset, the course or the
osis of the comatose state. Jaundice
ilirubinemia usually roughly parallel
tivity of the liver disease but do not
ny particular relation to hepatic coma
t that patients with active liver disease
ore likely to develop coma than those
he chronic, more stable variety. There
e a slight or even moderate rise in the
bilirubin concentration during the
ss of hepatic coma, but here again the
of bilirubinemia seems to parallel the
ss of the liver disease and not to be
d specifically to the onset or the dura-
f the coma.

e commonly used liver-function tests,
as the blood prothrombin activity, the
l turbidity, cephalin flocculation and
sulphalein retention likewise parallel
verity of the liver disease and are re-
to hepatic coma only insofar as they
ss the activity and the severity of the
disease. The urine urobilinogen is ex-
ly variable, and in a few cases reported
lly et al.[30] the nonurobilinogen Ehrlich-
ing substances were increased in the
to exceptionally high values. The blood
amino nitrogen concentration is usu-
ormal or slightly increased in hepatic
, except in patients with acute atrophy
e liver in which excessively high values
ound frequently. Except in this latter
nce, the total blood alpha amino nitro-
loes not bear any direct relationship to
nset, the course, or the prognosis. Meas-
ent of free phenolic compounds in the
d by Murphy et al.[42] were either normal
mewhat elevated but did not differ sig-
ntly from the values obtained in the
patients before the onset of coma. The
al or slightly elevated blood phenol val-
contrast with the high concentrations
d in uremia by Murphy et al.[42] and by
itt[46] and his colleagues.

outine examination of the urine is usu-
quite normal except for the changes in
e urobilinogen noted above and the pres-
of bilirubin when sufficient jaundice
esent to cause bilirubinuria. Small quan-
s of albumin and occasionally casts and other formed elements may be seen but are not observed with sufficient regularity or consistency to relate them to the comatose state. Generally then, it may be concluded that the routine examinations of blood and urine as well as the standard liver-function tests are related to the coma only insofar as they give evidence of severity and activity of the underlying liver disease. No one of them seems to be related clearly to the comatose state.

Hyponatremia and hypokalemia may be observed in patients with hepatic coma. The former is seen commonly in patients with liver disease without coma and usually is attributed to excess administration of water and to the powerful antidiuretic activity so frequently observed in these patients. It usually does not play a part in the genesis of hepatic coma. A few patients, notably those with oliguria, who are treated vigorously with sodium-free fluids, will develop acute and severe hyponatremia, and an apparent response in the state of consciousness appears following hypertonic saline administration and even partial correction of the hyponatremia. This is particularly true following paracentesis or other stimuli to antidiuresis. Hypokalemia is seen occasionally in hepatic coma. It usually does not arise spontaneously but is a reflection of overzealous treatment, particularly with cation-exchange resins not containing potassium. These matters will be discussed further below (Pathogenesis).

PATHOLOGY

Liver. Hepatic coma may arise as a complication and frequently as a terminal episode in patients with almost any form of severe primary liver disease. One would be right in expecting that the pathologic and histologic changes in the liver would be those of the specific liver disease from which the patient was suffering and not be particularly related to the state of consciousness. A comprehensive study has not been made of the pathologic changes in the liver in hepatic coma as distinct from patients with liver disease dying from other causes. On the basis of present evidence, however, there are no known specific changes in the liver attributable to or otherwise related to the state of consciousness of the patient. In Laennec's cirrhosis, for example, hepatic coma may arise and end fatally in patients with the chronic static form of liver disease in which extensive fibrosis is present, but relatively healthy-appearing liver cells are interspersed in islands between the extensive fibrous tissue. Perhaps more commonly the coma is a terminal event in the more active form with jaundice and leukocytosis[51] and in acute atrophy of the liver from poisoning or in pregnancy. In the acute form of liver disease described by Phillips[51] one finds the widespread areas of focal necrosis with polymorphonuclear infiltration and intracellular hyalin originally described by Mallory.[38] As hepatic coma may arise in patients with apparently quite static liver disease as well as those in whom acute liver disease is evident, the term "liver failure" should not be used as synonymous with hepatic coma, but only when there is clinical or other evidence of progressive disease.

Brain. Pathologic study of the brain and other nervous tissues has been made intensively by Adams and Foley.[1] They found little of diagnostic importance upon gross examination of the brain. Some jaundiced patients seemed to have a pale greenish hue to the dura. Various adventitious lesions, such as infarct and evidences of old trauma to the cerebral cortex, were observed. Wernicke's encephalopathy was found in two instances. Microscopically, an increase in number and size of the protoplasmic astrocytes was the characteristic and important finding. These large pale astrocytes were seen in

> all parts of the cerebral cortex, the putamen, globus pallidus, caudate nucleus, amygdaloid and sublenticular nuclei, thalamic and subthalamic nuclei, red nucleus, substantia nigra, tectum of the mid-brain, pontine nuclei, dentate and roof nuclei of the cerebellum, the purkinje layer of the cerebellum in some cases, the nuclei of Goll and Burdach, and the inferior olivary nuclei. The hypothalamic nuclei, interlaminar nuclei of the thalamus, and the somatic nuclei of brain stem and spinal cord were not involved to any significant degree.

The fibrous astrocytes in the white matter usually retained their natural appearance. The number of protoplasmic astrocytes was nearly doubled in the hepatic coma cases as
compared with the noncoma cases o
disease and the controls without liv
ease and they averaged about 35 p
larger in size. Degeneration of nerv
in the cerebral cortex thalami and len
red and dentate nuclei were observed
of the more severe and protracted c
hepatic coma. In some areas this was
ciated occasionally with a focus of
plasmic astrocytes. In the less sev
prolonged cases nerve cell loss or deg
tion was not as clear cut. Myelin
failed to disclose important abnorm
Specific changes in the oligodendrogli
those only of slight swelling. No s
changes in the blood vessels were ob
to be related to hepatic coma. Swollen
cytes were not found in the brains fr
tients who had had severe cerebral
uremia, diabetic acidosis, porphyria
rium tremens, Korsakoff's psychosis,
B deficiency or Wernicke's disease.
glycemia, fatal head injury, arsenic
soning, bacterial meningitis, or stat
lepticus. They felt that "the brain le
then highly characteristic of advance
disease, but is not specific." Atten
elucidate the cause of the swollen ast
were not productive of an answ
pointed to a metabolic defect affect
nervous system in these patients with
liver disease.

Kidney. The pathologic changes
kidney in hepatic coma have been litt
ied, in spite of the important rena
tional derangements so commonly f
this condition. Patients with intense
at the time of death may show the
"bile nephrosis," the significance of
not known. Many patients dying w
patic coma and severe liver disease s
tle or no specific pathologic change
kidneys.

Other Tissues. Specific changes
tissues either are not present or h
been found, other than as they
severe liver disease. Thus, bile sta
tissues is found in jaundiced patie
docrine changes, as they are obs
liver disease, will be found at auto
as yet no specific pathologic finding
sues other than the brain appear
lated to hepatic coma itself.

FFERENTIAL DIAGNOSIS

agnosis of impending hepatic coma
e made when a patient with liver
evelops mental confusion, the char-
flapping tremor, and (if possible)
tro-encephalographic changes de-
n the section on Clinical Manifesta-
hen the patient is in deep coma at
examination or when these charac-
igns are absent, the diagnosis may
asy, and differentiation from other
lesions must be made carefully. Any
the common conditions leading to
or example, brain tumor, a cerebro-
accident, diabetic coma or insulin
nay occur in a patient with severe
ease and be confused with hepatic
ccasionally even after careful study.
ic alcoholics with liver disease re-
ecial consideration in making the
of hepatic coma. This group of
is, of course, susceptible to delirium
acute alcoholic hallucinosis, Wer-
yndrome and Korsakoff's psychosis.
ntal confusion in Wernicke's en-
athy may resemble that seen in he-
ma, but the characteristic ophthal-
, the nystagmus and the ataxia that
ost always present in this condition
is full blown make the differentiation
epatic coma relatively simple. The
noplegia of Wernicke usually re-
within minutes to hours to the in-
us administration of thiamine. The
anifestations improve more gradu-
h alcohol abstinence and the provi-
an adequate diet. The manifestations
um tremens are well enough known
equire detailed consideration in the
iation from hepatic coma. The
of delirium tremens is much more
nd is accompanied by a degree of
n and motor activity uncommonly
hepatic coma. Hallucinations and
s so regularly seen in acute alcohol
wal are rare accompaniments of he-
oma. The memory defect and con-
on which are characteristic of Korsa-
sychosis are not components of he-
ma, although peripheral neuritis may
ent in any alcoholic with or without
iver disease.

Cerebral trauma in a patient with manifest liver disease may be confused easily with hepatic coma. It is particularly important to recognize this because many alcoholics develop severe liver disease and also are often subjected to head trauma. Moreover, the lowered prothrombin concentration, the reduced platelet count and other hemostatic abnormalities so commonly found in liver disease may cause severe or progressive bleeding following even minor trauma. If possibility of previous trauma exists, and if there are progressive disturbances in consciousness leading to coma, a skull fracture with either brain contusion or laceration should be suspected, and prompt measures taken to make the diagnosis.

The cerebrospinal fluid as examined by the usual tests is found to be normal in most patients with hepatic coma. Adams and Foley examined the spinal fluid in more than 25 cases and found the pressure to be normal, no cells and the protein content within normal limits. Xanthochromia was present in a few patients with intense jaundice. Walshe[75] has found an abnormal content of amino acids in hepatic coma.

Perhaps the most important traumatic cerebral lesion confused with hepatic coma is subdural hematoma. In this case the traumatic history may be insignificant or so long in the past as to be forgotten. The mental confusion associated with a subdural hemorrhage is sometimes indistinguishable from that of impending hepatic coma. A penetrating history taken from the relatives of the patient may lead to the history of trauma, and careful and repeated physical examinations must be made in an effort to find localizing signs. However, even a history of trauma, together with localizing signs, may be a concomitant of hepatic coma as noted above (Clinical Manifestations), so that even conscientious and painstaking clinical examination may not serve to differentiate these two—indeed, the two may co-exist occasionally. Finding erythrocytes, especially if crenated, in the spinal fluid may support the diagnosis of subdural hemorrhage. If a reasonable suspicion of subdural hematoma exists, burr holes should be made with a careful search for a clot.

As discussed in the section on Clinical

Manifestations, the tremor of Wilson's disease resembles somewhat that seen in impending hepatic coma. In the former, however, the tremor is usually greatly exaggerated and has other characteristics that may serve to differentiate it from the latter. Moreover, the tremor is of long duration, and mental confusion is not a part of Wilson's disease at least until the terminal stages. This differential should not be difficult to make.

PATHOGENESIS

The pathogenesis of hepatic coma is not known, but because it is an affliction of the central nervous system in patients with severe liver disease these two organs and their interrelationships must be studied carefully.

Discussing first the brain, it may be said that hepatic coma is in essence a progression from confusion to stupor and then unresponsiveness, and that the only consistent and significant pathologic lesion found in the brain is an increase in number and size of the protoplasmic astrocytes (see p. 240). The similarity of certain aspects of hepatic coma to the clinical manifestations of Wilson's hepatolenticular degeneration might be of some help were the etiology of the latter condition known, but it is not. The abnormalities in copper metabolism observed in Wilson's disease seem to be specific for that disease and are not evident in patients with severe cirrhosis of other etiologies unless to a minor degree. Considering the clinical manifestations of hepatic coma, one is led to look either for an excess of some "toxic" substance affecting the brain or for a deficiency of a metabolite necessary for nervous tissue. Although there are many disturbances in intermediary metabolism in patients with severe liver disease and especially in hepatic coma, no substance has yet been positively implicated, either in excess or as a deficiency in the pathogenesis of this condition.

Turning to the clinical manifestations and abnormalities in laboratory measurements in liver disease, we find little additional help in elucidating the pathogenesis of hepatic coma. The fact that it may occur as a complication of any of the many forms of severe liver disease eliminates as etiologic agents abnormalities that occur in certain spec forms of liver disease. Thus, marked ami acidemia is characteristic of acute atro of the liver but is not seen in the coma patients with cirrhosis.[42] Using the tech of paper chromatography, Walshe[75] has served distinct abnormalities in the bl content of individual amino acids. Hy glycemia with coma is an occasional find in hemochromatosis but is rarely seen in usual patient with hepatic coma, and spec treatment with glucose solutions fails to a the state of consciousness except in the tremely unusual instances in which hy glycemia does occur.[42] As noted earlier, term "cholemia" has been applied to hep coma, suggesting a flooding of the blood w materials such as bilirubin and bile s which are usually excreted by the liver i the gastro-intestinal tract. Hepatic coma quently occurs in the absence of bilirubi mia or other evidences of biliary obstruct so that failure of the liver to excrete th substances cannot be implicated as an portant etiologic factor.

The usual liver-function tests (e.g., br sulphalein, cephalin flocculation, thy turbidity and flocculation, and prothron concentration) do little more, as a rule, t demonstrate that severe liver disease is p ent. They offer no help in deciding whe hepatic coma will occur or not. Moreover specific change in the already deranged li function tests occurs when coma superve except as they become more abnorma cases of progressive liver disease, suc acute atrophy or necrosis. The ordinary tient with cirrhosis will have little if change in these tests when they are pared before and in deep coma. A slig occasionally moderate rise in serum bili concentration may be observed, but monly there is no change at all. The of aid from these tests in understandin patic coma may be due to their nons ficity. In fact, of the many important bolic functions of the liver, few are ame to careful clinical investigation.

A number of metabolic abnorm have been studied in severe liver diseas some may be particularly deranged i patic coma. Whether or not any one or of these is related to the pathogene

oma remains to be proved. Elevated
pyruvate and lactate were observed in
c coma by Snell and Butt.[64] Recently,
uzio et al.[2] found only minor abnor-
es in blood pyruvate concentration
glucose administration to conscious
ts with severe liver disease. However,
ients with hepatic coma after intrave-
glucose had a progressive and marked
f blood pyruvate, suggesting a block in
etabolism of this keto acid. The glu-
tolerance curve was normal. A de-
cy of thiamine which, as cocarboxylase
osphothiamine), is necessary for the
olism of pyruvate may account for this.
an explanation is improbable, however,
ge amounts of thiamine are almost in-
bly administered to patients with severe
disease, particularly those with coma,
ut evident therapeutic benefit. The pos-
y that thiamine is poorly converted into
boxylase has not been investigated in
ic coma and seems to be a fruitful ap-
h. In this connection Williams et al.[79]
demonstrated a partial defect in thia-
phosphorylation in chronic cirrhosis.
substances in the Krebs cycle have not
studied in hepatic coma, except that
et al.[63] found a distinct rise in blood
-keto-glutarate concentration in severe
disease.

r a long time the metabolism of am-
a has been studied by biochemists in
on to the liver[56, 66] and recently has
investigated more intensively in regard
e possibility of its playing a part in the
is of hepatic coma. One of the most
rtant functions of the liver is the re-
l of the toxic substance, ammonia, and
nversion to urea. Much early work sup-
d this concept; for example, the portal
blood of dogs was found to be much
r in ammonia than that in the hepatic
[27] Moreover, an increase in ammonia
e blood was found in dogs after an
fistula.[44, 20]

a series of brilliant studies of the com-
ly hepatectomized dog, Bollman, Mann,
ath and collaborators[6, 7, 8, 30] clearly
onstrated the role of the liver in deami-
n of amino acids and urea formation
ammonia. They found a high blood
onia content in the blood of these hepatectomized dogs which they believed arose largely from the gastro-intestinal tract. The decrease in blood urea concentration after hepatectomy in dogs was found to be abolished if bilateral nephrectomy were done also.[7] In this circumstance the concentration of blood urea remained unchanged, indicating no further formation of this substance after the liver had been removed. Finally, the demonstration by Krebs and Henseleit[34] that liver tissue alone was able to form urea from ammonium salts established the liver as the site of urea formation as originally suggested by von Schroder.[72]

The development of anorexia, emesis and lethargy after Eck fistula or hepatectomy in dogs that had been fed protein, substantiated the concept of "protein intoxication." It was considered that protein breakdown products in the gastro-intestinal tract were absorbed and not removed in these animals. Because of its toxicity ammonia was considered as one of the possible causes of this phenomenon.

J. Monguio and F. Krause[41] studied the significance of the blood ammonia content as a method of evaluating liver function. They studied dogs—normal, with liver injury and after an Eck fistula. High blood ammonia concentrations were found after chronic meat feeding, and the term "meat poisoning" arose. The authors note:

> In the event that our opinion that a meat diet produces ammonia poisoning in dogs whose livers have been injured should be verified by experiments, then it will become urgently imperative that all patients suffering from functional disturbances of the liver, especially cases of severe injuries to the parenchyma and cirrhosis, should have protein food reduced to small portions.

A somewhat simplified summary of the metabolism of ammonia may be helpful. If we follow a molecule of NH_3 arising from ingested ammonium salts or produced by bacteria in the gastro-intestinal tract, we find it absorbed into the portal circulation so that normally it is presented at once to the liver. Most of the ammonia is removed from the portal blood by the liver so that little if any escapes into the general circulation. Ammonia which is sometimes formed by the other tissues, especially under conditions of anoxia, is also removed from the blood by the liver. By far the largest amount of ammonia is converted to urea. Urea formation probably is accomplished through the "ornithine cycle." Ammonia and carbon dioxide first combine with glutamic acid, forming carbamylglutamic acid. The carbamyl group is transferred to ornithine, which adds another ammonia to form arginine. The enzyme arginase, present in considerable amounts in the liver, splits off urea from arginine, and ornithine is reconstituted.

The toxicity of ammonia is well established. Ammonium salts given intravenously to animals produce convulsions and death. Moreover, the intravenous administration of urease which rapidly converts blood urea to ammonia and produces a rise in blood ammonia concentration is also fatal after convulsions.[12, 65] It is interesting to note that the effect of urease can be prevented by the prior immunization of the animal with small but gradually increasing doses of crystalline urease which incites the formation of a powerful antiurease.[32]

Elevated blood ammonia concentrations in patients with diseases of the liver have been reported by a number of observers.[22, 31, 33, 70] Patients with severe Laennec's cirrhosis after the ingestion of ammonium chloride or urea by mouth may develop drowsiness, confusion and clonic muscular jerkings.[52, 69, 71] These symptoms usually were associated with elevation of the blood ammonia concentration. The rise in blood ammonia concentration found by van Caulaert et al.[69] after the ingestion of ammonium chloride by patients with atrophic cirrhosis was believed to be due to the shunting of blood through collateral channels to the general circulation, avoiding the liver. Whether or not ammonia exists in the blood as such under normal circumstances has been a matter of considerable controversy. Likewise, the high blood ammonia values found in some patients with liver disease, especially after the ingestion of ammonium salts, may not be due to free ammonium ion present but may come from ammonia that is liberated from other nitrogenous substances during the distillation in the process of ammonia determination. Kirk,[31] who studied ammonium tolerance in patients with liver disease, felt that, although the tolerance seem be reduced, the symptoms following a nium ingestion were due to acidosis was not substantiated by the more observations of Phillips et al.[52] ar Schwartz et al.[57]

Fuld[22] in a discussion in the use of ammonia determinations in the diagn liver disease stated:

> According to our results, therefore, n blood ammonia values do not always e cirrhosis of the liver at a time when the has not progressed too far and the amou protein in the diet are exceptionally h Generally, the increase of ammonia blood also paralleled an increase of u ogen in the urine. Nevertheless, we were able to determine this increase at a time no other symptom yet pointed to liver d

Contemporary studies in patients w vere cirrhosis[52] and in a patient with a fistula[37] have shown quite clearly th syndrome of impending hepatic com even deep coma may be induced by t ministration of ammonium chloride. monium citrate, urea and even occas after increases in dietary protein. Al ammonium chloride did induce acido ammonium citrate did not in the sa tients, thus eliminating acidosis as an tant factor. Following the administra these nitrogenous substances, blood nia concentrations rose in most but of these patients. Patients with spon hepatic coma likewise have been show ally to have elevations of the blood a concentration which is in most in but not all, above that observed in with severe liver disease but withou bral manifestations.[68] The correlat tween the state of consciousness blood ammonia content is not sat enough to establish a firm etiologic ship.[52, 57, 68]

The failure to find a consistent co between blood ammonia values symptoms and signs of hepatic co mean that the methods for measurin ammonia are not specific or sensitive that it is tissue rather than blood which exerts the toxic effect, or that monia absorbed is converted to so presumably more toxic substanc

at further investigation will eluci-
discrepancy.

ear from the foregoing that ammo-
lts and certain other nitrogenous
s, especially protein, taken by
may be quite harmful to patients
re liver disease as they may lead to
g hepatic coma or even deep coma
h. From our present knowledge of
emistry and the bacteriology of the
testinal tract it is fair to assume that
onium salts are absorbed as such,
high in the gastro-intestinal tract.
d protein taken by mouth presum-
t be changed to ammonia by the
tting organisms in the small intes-
the colon.

uld be noted that all patients with
ver disease to whom these nitroge-
stances are administered do not de-
patic coma. In fact, the proportion
is probably small. Nevertheless, al-
is reaction does not occur regularly
mechanism is obscure, the adminis-
y mouth of ammonium salts or urea
ics or large amounts of dietary pro-
ld be undertaken only after careful
nt of their possible toxicity and the
d of effectiveness. When administra-
lecided upon, the physician should
his patient carefully and frequently
ch for the early signs of impending
coma. Should these appear, the pre-
ffending substance should be omit-
with respect to dietary protein,
in amount. This will be discussed
under the section on Treatment.

mine is formed in the liver by the
of ammonia to glutamic acid. Weil-
e[78] considers glutamine a sort of
g system in which glutamine is
when too much ammonia is present
nonia is liberated for other reactions
e opposite circumstance is in effect.
nd his colleagues[18] observed a very
tamine content in the brain of dogs
fter hepatectomy. Walshe,[75] using
hromatography, found a marked in-
f glutamine in the blood and particu-
cerebrospinal fluid of patients with
coma. However, Seegmiller and his
es[58] were unable to show any cor-
between the blood glutamine content and the state of consciousness of the patients. In fact, the blood glutamine seemed much less likely to parallel the clinical manifestations of hepatic coma than did the blood ammonia concentration.

There is a high concentration of glutamic acid in brain tissue, and Weil-Malherbe[78] has shown that glutamic acid will sustain the respiration of brain slices and will itself be oxidized. Presumably, glucose is the usual metabolite for brain tissue, but under certain circumstances it may be that glutamic acid is metabolized to a considerable extent as well. Glutamic acid also enters into transamination with the formation of other amino acids and of alpha-keto-glutaric acid. It may be noted that several coenzymes, many of which must be phosphorylated before they are active, are necessary for the enzymatic reactions involved in ammonia removal and metabolism. Moreover, many of these reactions require energy, specifically high-energy phosphate.

When these reactions are not functioning properly, either due to deficiency of coenzymes, of high-energy phosphate, of energy-producing reactions, or because the portal blood by-passes the liver through anastomotic channels, ammonia toxicity could easily result. It is not surprising, therefore, that disturbances in ammonium metabolism have been studied extensively in patients with severe liver disease.

Ammonia is formed in the kidney by the action of glutaminase upon glutamine and perhaps also by deamination of amino acids. Ammonium salts form a small portion of the nitrogen in the urine under the usual circumstances, but an increase may occur when it is necessary to excrete a cation to conserve fixed base, specifically sodium.

Kidney function in patients with hepatic coma has been studied insufficiently. Murphy et al.[42] and Schwartz et al.[57] found oliguria and moderate azotemia to be common although not universal concomitants of hepatic coma. In fact, during its development or at some time before termination most patients become oliguric with a rising blood nonprotein nitrogen concentration.[40, 45, 54] The rise in nonprotein nitrogen is due almost entirely to a rise in blood urea concentration and is due almost surely to the oliguria. The decrease in urine volume usually persists in spite of an adequate water intake and severe sodium restriction and, therefore, in these circumstances, is not due to dehydration or to fluid retention because of failure of sodium excretion. When more fluids are administered to such a patient than his kidneys will excrete, progressive fluid accumulation will occur. When fluid intake is high, and when oliguria is marked and severe sodium restriction is adhered to, an increase in extracellular water and consequent dilution of the extracellular electrolytes occurs. Hyponatremia and occasionally hypokalemia may be seen in this circumstance. As will be noted in the section on Treatment, beneficial effects may follow the correction of these electrolyte disturbances. The cause of the frequent and usually marked oliguria in these patients with hepatic coma is not known. Whether increased amounts of the posterior pituitary antidiuretic hormone are produced or whether the severely damaged liver under these circumstances diminishes its metabolism or inactivation of this hormone is not known, but both of these are possible causes which have been postulated with some experimental backing to account for the oliguria.[54]

The production of a vasodepressor substance VDM by the anoxic liver has been demonstrated by Shorr and colleagues.[62] This substance also has a powerful antidiuretic activity. Whether it is increased in activity in patients with severe liver disease, especially those with hepatic coma, is not known. Nevertheless, it is possible that an increased production of VDM may be one of the factors accounting for the oliguria. That it is not the only factor seems reasonable from the observation that hypotension which should be observed with increased VDM activity is not the rule with hepatic coma, although it must be admitted that reduction in blood pressure may occur during the genesis of hepatic coma.

Some patients who develop spontaneous hepatic coma—that is, in whom no exciting cause is found—are observed to maintain a perfectly normal urinary output, do not have a rise in blood ammonia or nonprotein nitrogen concentration and have a normal electrolyte balance. In fact, in these patients no physiologic or biochemical abnormalities observed except for the development of d coma which may be fatal. Careful obser tions of patients of this kind leads one believe that, although the factors outli above may be important in the genesis hepatic coma, other disturbances not yet fined and studied probably exist and may of subsidiary or even of primary importa in the pathogenesis of hepatic coma.

TREATMENT

PREVENTIVE

Most patients with severe liver dise appear to develop coma quite spontaneou From the discussion in the section on Pat genesis it is evident, however, that a hos factors may predispose toward, hasten development of, or actually induce this quently terminal complication in pati with severe liver disease. The relation these factors to the genesis of hepatic c will become clearer as more is known of condition. Even at the present time it is sible to find for the majority of patien predisposing event or factor which may etiologically important and might have correctable or avoided. It behooves the sician, therefore, to become familiar wit of the possible predisposing agents mechanisms so that they can be avoide far as possible. It is not practical unde circumstances to avoid all of these pos factors because some of them, such as centesis, are necessary for the treatme other manifestations of chronic liver dis and others, for example, massive gastro-intestinal hemorrhage, are not classifiable as preventable conditions.

The Use of Hypnotics, Analgesics, tives and Anesthetic Agents in Liver ease. All of the common hypnotics, sed and analgesics may be tolerated poorl even contribute to the induction of h coma in susceptible patients.[42] Often agents are needed by the patients who s not receive them. The excitement, the irrational and inappropriate behavi often observed especially at night early stages of hepatic coma urgently r that a sedative be given in order th patient, his neighbors, or the doctors a

may find relief. Frequently, it is in
rcumstance after the administration of
lative that stupor and then deep coma
r and may become irreversible and
tally. Whether the sedative in this cir-
ance actually induces hepatic coma or
y accelerates progression into deep
has been debated and is not known.
ever the answer, however, there is no
that many patients with early or im-
ng hepatic coma who are given a seda-
pidly develop coma that may be irre-
le. The same chain of events may
less commonly in patients with severe
disease who have no evidence of im-
ng hepatic coma. Therefore, the physi-
must exercise extreme care in the ad-
ration of sedatives, analgesics or hyp-
to patients with severe liver disease.
theless, under certain circumstances
on is necessary, and one should know
agent to choose and what dose to ad-
er. Before deciding it might be well
cuss briefly the pharmacology of these
with particular reference to their me-
sm by the liver.

rphine and some of its closely allied
tives are probably the worst offenders
genesis of hepatic coma.[14, 29] Mor-
is conjugated in the liver before it is
ted.[4, 47, 48] Gross[25] found the conjuga-
of morphine in animals greatly de-
ed after liver damage. In man the dura-
of action of morphine is prolonged in
nts with severe liver disease. It is not
nmon to find that such a patient given
tle as ⅛ grain of morphine will sleep
day or two. It is probable that metha-
is in a class with morphine in patients
liver disease, as it appears to be metab-
l by the liver also.[10] In contrast with
hine and presumably methadone, Dem-
does not appear to require the liver for
cretion; or, if it does, the requirement is
titatively much smaller than for mor-
.[76] It seems possible to give compara-
larger doses of Demerol to patients
severe liver disease without inducing
nged sleep. In addition to its prolonged
n morphine has a second contraindica-
that of its antidiuretic action.[23] Whether
oliguria so commonly seen in hepatic
is cause or effect is not clear. Nevertheless, accentuation of the oliguria by morphine administration would seem to be poor clinical practice. The use of the new antidote for morphine poisoning, *N*-allylnormorphine,[3] has not been documented in the treatment of morphine poisoning in patients with severe liver disease; but, considering its effect in other instances of morphine poisoning, a fair trial should be given.

There is good evidence for the generalization that the long-acting, short-chain barbiturates are excreted largely by the kidney while those with a more rapid onset and shorter action and larger molecules tend to be handled by the liver.[11, 53, 55] The thiobarbiturates (for example, Pentothal Sodium) are also detoxified by the liver.[61] Therefore, if barbiturates must be used, one should choose those with the greatest renal excretion, such as barbital and phenobarbital. Pentothal and pentobarbital presumably would be among those less easily handled in patients with severe liver disease. Whether there is, in fact, any delay in handling the various barbiturates in patients with severe liver disease as compared with normal individuals seems to be doubtful from the work of Sessions et al.[59] Nevertheless, patients who have been given either frequent small doses or a relatively large dose of a barbiturate have developed hepatic coma; whether coma was induced by the barbiturate or the process was accelerated is not known. Of course, a great many patients with liver disease have been given barbiturates without the development of hepatic coma. Moreover, the need for hypnotics is great enough that barbiturates will have to be given in many circumstances irrespective of the possible development of hepatic coma. The physician who recognizes the possibility of coma will guard the dosage and the frequency of administration much more carefully.

Perhaps almost as bad an offender as morphine is paraldehyde, both because it presumably is metabolized to a considerable extent by the liver and because it is used so often as a sedative in alcoholics who may have severe liver disease.[35] Many instances of hepatic coma have been seen which appear to have been induced or accelerated by the administration of paraldehyde. Demerol and the barbiturates which are excreted largely by the kidneys seem so much less harmful than paraldehyde that little indication exists for the administration of this drug to patients with severe liver disease. When paraldehyde has been used, often one can detect the characteristic odor on the breath for several days, indicating its slow elimination from the body.

Although it is a chlorinated hydrocarbon, there seems to be little reason to believe that the small doses of chloral hydrate used as a sedative would produce further liver damage. It is considered that chloral hydrate is conjugated by the liver and hence is also presumably not a satisfactory drug for use in patients with liver disease. The mild hypnotic effect of the bromides which presumably are excreted almost entirely by the kidneys might be useful in these patients.

As a general statement it can be said that the dosage for most of the hypnotic sedatives and analgesics should be considerably less for patients with severe liver disease than for normals, both in quantity given and frequency of administration. For example, 50 or even as little as 25 mg. of Demerol may give a satisfactory analgesic effect. The barbiturates do not appear to be as effective in smaller than usual doses, but their frequency of administration must be controlled carefully. Instances of prolonged sleep have occurred following the continued administration over several days of as little as a half grain of phenobarbital 3 times daily.

In conclusion, the use of analgesics, hypnotics and sedatives in patients with severe liver disease may be hazardous. When their use is clearly indicated, care should be given to the dosage and the frequency of administration, and prior to this the patient should be examined carefully for evidences of impending hepatic coma.

It has long been known that patients with liver disease tolerate surgical operations poorly. This may be due in part to the prior administration of hypnotics and analgesics. Only under rare circumstances should morphine be used, particularly as Demerol seems to be a safer substitute. Again, dosage of these agents should be reduced, particularly with regard to their frequency of administration.

The effect of anesthetic agents on the liver has not been studied extensively, altho it is well known that chloroform particul as well as some of the other inhalation a thetics, will produce liver damage. Fa and colleagues[15] found abnormalities bromsulphalein excretion after surgical o ation and anesthesia with ether, cyclop pane and spinal. The bromsulfalein excre can be decreased in febrile states, shock, in a number of other circumstances, part larly when the circulation to the liver is tered, as well as after liver damage itself that this test may not be an entirely criterion of the effect of the anesthetic ag Certainly chloroform never should be in patients with liver disease, if it is adv under any circumstances. Whether ethe more harmful to the liver than the o commonly used inhalation anesthetics been debated. Some consider that cyclo pane is less harmful than ether.[5] As many other medications in liver dis anesthetic agents should be used only absolutely necessary and then with caution and respect.

Acute infection is an important pre tating factor of hepatic coma. All acut fections in patients with liver disease sh be handled with great care and preci and when the patients are susceptible appropriate antibiotics should be used i usual therapeutic amounts (possible sp actions of antibiotics will be discusse p. 254). In addition, every effort shou made to keep the patient's urinary o satisfactory during a febrile episode though overloading with fluid shoul avoided when oliguria not associated dehydration is present.

Ammonia Metabolism. From the d sion in the section on Pathogenesis con ing the relation of ammonia metaboli hepatic coma it is evident that grea should be exercised in the administrat ammonium salts or urea as diuretics tients with liver disease. It is true only a small number of these patien develop hepatic coma with the admi tion of ammonium salts, so that the be used as diuretic agents when nec particularly in patients with milder fo liver disease and if careful watch patient's condition is made. Eviden

confusion and of the characteristic
should be searched for at frequent
s when these substances are given.
no circumstances should they be given
rely ill patients or particularly to those
gns of impending hepatic coma. The
n of dietary protein will be discussed
under Therapeutic Measures.

e gastro-intestinal bleeding is an im-
predisposing factor in the genesis of
coma. The bleeding may be from
d esophageal varices, from peptic
which is more common in patients
er disease than in those without, from
s (particularly in alcoholics) or less
nly from other sites. Patients with
liver disease may bleed extensively
cover after transfusions and other
utic measures, only to lapse into
rom 24 to 48 hours later. The etiology
coma in this circumstance probably
ed to the two factors of blood loss
tendant shock and oliguria, to other
lic aberrations and to the large
t of protein deposited in the gastro-
al tract which may release ammonia.
ent should be aimed at therapy for
with blood transfusions and other
es, stopping the bleeding, and when
al removal of the blood from the
y enema.

always an extremely difficult problem
ide whether an emergency operation
be done in a patient with severe liver
who has upper gastro-intestinal tract
g. The decision must be made on a
individual basis after careful consul-
between surgeon and internist, and
nly when the patient's condition has
ed and there is some hope with a rela-
brief operation of preventing a recur-
of the bleeding.

centesis. To a lesser degree the same
on exists with respect to paracentesis
e removal of ascitic fluid. Although
minor surgical procedure, the meta-
complications may play a part in the
s of hepatic coma which follows all
equently within 24 to 48 hours after
ntesis in patients with severe liver
e. Reduction in plasma volume and
a are usual after removal of large
ties of ascitic fluid from the peritoneal cavity. They are due presumably to the rapid reaccumulation at the expense of the plasma of a small volume of ascitic fluid within the first few hours after paracentesis. Hyponatremia, particularly when sodium intake is restricted, may follow the ingestion of water during this period of oliguria. These factors may play an important part in producing impending or even deep hepatic coma following this procedure. The physician is wise to be cautious before undertaking paracentesis, although when dyspnea or severe anorexia can be relieved by paracentesis, probably it should be done. If the patient is in the early stages of hepatic coma, the decision becomes an extremely difficult and an individual one. It may be that in this circumstance the removal of small quantities of fluid from time to time would accomplish the same result more slowly but with less likelihood of upsetting the metabolic balance.

GENERAL THERAPEUTIC MEASURES

Exacting nursing care is a *sine qua non*, particularly when deep coma is present. Not only general measures are important, such as keeping the patient clean, preventing decubitus, etc., but also the highly important measurements of intake, output and the vital signs are of the utmost value in following these patients. Without these measures there is little chance that the physician will be able to make the essential calculations necessary to understand what has occurred to his patient. The optimum treatment of hepatic coma could be accomplished most easily on a metabolic ward with trained personnel and complete laboratory aid, but these facilities are seldom available. However, good nursing, the usual laboratory facilities and an attentive physician should be as satisfactory.

The first principle in the treatment of hepatic coma is that of meticulousness by all personnel concerned: care for the patient's general condition, care that all that happens to the patient is known and recorded, and care to observe, record and treat all complications. In this way the treatment of hepatic coma is much like that of diabetic coma except that a specific treatment, such as insulin, is lacking. A flow sheet for the recording of clinical and laboratory data, including the intake of fluid, electrolytes and nutrients, and the volume of urine and the quantity of feces is essential. All observations should be made at frequent intervals, beginning at the earliest possible stage of the disease—during impending coma or earlier, if this can be done. The following observations are among those considered important in following a patient with hepatic coma.

Clinical Observations. These should be made once daily unless the clinical state is changing rapidly, in which case more frequent, even hourly, examinations should be made. The extent and the magnitude of the characteristic tremor should be recorded, and the state of consciousness classified approximately according to Table 19. When the patient no longer responds, the deep tendon reflexes, the sucking, grasping, plantar and corneal reflexes should be examined. Minor degrees of mental confusion are difficult to evaluate. Simple mathematical problems, such as subtracting sevens from 100, will sometimes bring out a mild confusional state when the patient answers correctly the questions as to time, place and person. Sometimes, even though the patient gives satisfactory answers to the usual questions, a slight clouding of consciousness is apparent by the relative slowness with which the answers are given. A certain untidiness about the person himself and his belongings is sometimes observed. Inappropriate behavior may be a clue to early hepatic coma, and often a curious staring, glassy-eyed appearance of a patient is evident—the so-called "faraway" look described by Phillips.[50]

Intake and Output. The intake and the output of all fluids, electrolytes and nutrients must be listed. From this it is possible to make a satisfactory judgment of the patient's fluid and electrolyte balance and to observe whether or not the caloric and protein requirements are being met. The urine volume and specific gravity should be recorded, and the volume tallied at regular intervals. Insensible loss of fluid should be estimated, and the amount of fluid contributed by the oxidation of food should be calculated. In this way an intake and output balance sheet can be maintained, and one will not err on the side of dehydration or of fluid intoxication. If the patient is incontinent of urine, or
if there is other reason to doubt that col
tions will be complete, an indwelling cath
with constant drainage should be use
spite of the possibility of bladder or r
infection. Daily irrigations with a 1:1
dilution of Zephiran solution are often
fective in preventing infection.

Laboratory Observations. Daily dete
nations should be made of the blood hem
crit, the blood nonprotein nitrogen con
tration, the blood carbon dioxide con
and when possible the body weight.
hematocrit will serve as another inde
possible hemoconcentration or hemo
tion, and the nonprotein nitrogen and
blood carbon dioxide combining power
helpful in estimating the ability of the
neys to clear the end-products of nitr
metabolism and regulate the acid-base
ance of the body. When possible, it is
sirable to measure the serum sodium-p
sium-and-chloride concentration. As
earlier, hyponatremia is common in he
disease, especially when ascites is pre
In hepatic coma hyponatremia somet
becomes profound, particularly follo
paracentesis or after large quantities of
are given. The blood sugar should be
ured occasionally, particularly early i
course to eliminate the rare hypogly
as a causative factor (see p. 242).
stool passed should be examined, if pos
for the presence of blood. It is some
useful to know the total daily sodiu
cretion so that a kind of sodium balan
be achieved. Most patients with ascite
edema can be assumed to excrete onl
nute quantities of sodium daily. Ho
in other situations sodium may be ex
relatively normally and occasionally
cess quantities, especially when chroni
disease is also present.

Intake of Electrolytes, Water an
trients. If the patient is in semicoma
coma and cannot eat or be fed satisfa
a stomach tube may be used. A patie
has bled recently from esophageal va
has had another cause for upper
intestinal hemorrhage should not b
bated, but the mere presence of var
x-ray or their suggested presence be
portal hypertension or the severity
liver disease need not contraindicate

lubricated, there seems to be much
ger from intubation than from with-
food.

venous feedings may be used when
or necessary. At present, because of
nce of adequate supplies of a suita-
emulsion for parenteral use, calories
difficult to supply intravenously in
t amounts. Glucose, saline solution
otein hydrolysates may be given,
areful to judge the required fluid and
yte intake as well as that of the other
s. A word about a possible specific
f glucose will appear later in the
(see p. 253). When solutions are fed
or intravenously, their rate of ad-
tion should be relatively slow so that
and other tissues are not flooded at
ith large quantities of nutrients.

M. If ascites and edema are present,
intake should be restricted to ap-
tely 200 mg. per day or less. When
one, it is essential to follow the fluid
nd output, the blood hematocrit and,
ble, daily sodium excretion, so that
remia and sodium depletion do not
f ascites and edema are not present,
e quantities of sodium can be ad-
ed, again constantly watching the
balance if possible, but at least care-
lowing the fluid balance and the body
If sodium administration leads to
ned urine volume and gain in weight,
be assumed that fluid is being retained
t ascites and edema will put in their
nce. In this circumstance sodium re-
should be begun before these clini-
lences are apparent.

ER. Many patients with chronic liver
have a decreased tolerance to water.
nds to be much more marked in pa-
vith hepatic coma. It is wise, there-
order to avoid water intoxication and
remia to restrict somewhat the fluids
tered to patients with impending or
epatic coma. Most patients are able
care of approximately 2,000 cc. per
the urine volume is low, one should
dehydration, a marked decrease in
olerance, or severe hyponatremia and
depletion. It is in this complicated
tance that accurate records of fluid
and output and fluid balance are invaluable. If relatively large quantities of fluid have been given and if the blood hematocrit has been falling, one can suspect overhydration and hyponatremia. A very low serum sodium concentration corroborates this hypothesis, but even in the absence of this measurement and on clinical grounds alone one may decide to administer hypertonic saline in an effort to bring about an electrolyte concentration closer to normal, and perhaps one may even promote diuresis. This treatment of hyponatremia has effected a striking improvement in the state of consciousness of occasional patients with hepatic coma.[43] If the urine volume is low, and if fluid intake has been restricted severely, one can suspect dehydration, and an increase of fluid intake can be given a trial for 24 hours; but if such an increase in fluid intake does not lead to a concomitant and proportional increase in urine output, it is evident that the patient has a greatly reduced water tolerance. In this circumstance continuing the high fluid intake will lead inevitably to fluid retention, hemodilution and hyponatremia.

Calories. The caloric requirements for patients in hepatic coma are not known and are difficult to estimate. It seems safe to assume that unless the patient is extremely restless or has a high fever the energy expended will not be high. Approximately 2,000 calories per day would seem to meet the needs of most patients. If fever or muscular agitation are present, a higher caloric intake should be provided. The reason for attempting to cover the body's energy needs is to prevent body protein from being burned for energy with the release of nitrogenous products which the liver may have trouble in converting to urea and the kidney difficulty in excreting, particularly if oliguria is present.

Protein. The physician is on the horns of a dilemma in trying to decide how much protein to feed to a patient with hepatic coma. If on the one hand he gives too much, it is possible that the coma may be made worse (see p. 243). If on the other hand he should err and give too little, all the bodily processes depending upon protein for their function will suffer; specifically the liver, which needs protein for healing, will not receive the optimum treatment. With our present state of knowledge it is impossible to lay down strict or definite rules for the protein intake of such patients. It is a good rule to begin one's thinking with the National Research Council's Food and Nutrition Board recommended dietary allowances of 1 Gm. of protein per kilogram of body weight per day. If on this intake the patient becomes worse or if there is reason to believe that food protein played a part in the genesis of the hepatic coma, a reduction of protein intake may be contemplated. The minimum requirements of protein for a normal individual are not entirely known, but Hegsted and colleagues[26] estimate that, if animal protein forms a reasonable proportion of the diet, the normal individual can maintain nitrogen balance with about 30 Gm. or slightly less per day. It seems wise as a minimum to provide more than this to patients with hepatic coma, even if protein is implicated in its genesis, so that perhaps from 40 to 50 Gm. per day should be given as a minimum. However, if protein is implicated clearly in the genesis of hepatic coma, it may be wise to eliminate protein from the diet altogether for a short period of time, presumably for not more than a day or two. Occasionally, patients will appear to respond to this abstinence from protein with a decrease in signs of hepatic coma.

It is not always easy to find foods that can be taken by the patients with severe liver disease and still supply what the doctor desires. In general, frequent small feedings of a liquid mixture seem to be most satisfactory. The simplest basis for such a mixture is whole milk, preferably homog
When sodium intake must be restric
low-sodium milk product, such as "
lac,"* can be given. Eggs and some k
simple carbohydrate material, such as
trimaltose,"* can be used to bring
protein and caloric intake to the
level. Small amounts of cream may be
sary to reach the desired calories.
amounts of cream or other fats som
are not tolerated well by patients wi
disease, because they cause diarrhea

Vitamin Administration. This is sel
problem in these patients, as most o
receive large or even massive doses o
mins as a routine. It seems well to su
least adequate amounts of the com
administered vitamins, either orally
enterally, particularly if the patient ha
to the hospital after a heavy drinking
or with an unknown dietary history
of poor food intake. It is doubtful tha
patients will respond to large doses
mins, since there is little or no evid
vitamin deficiency in most patients wh
been in the hospital for a time. Ne
less, the remote possibility that som
may accrue from large doses, either b
action or in some other way, does n
traindicate their use. However,
doses need not be given. It is sugges
approximately the quantities of the
recommended by the Committee on
peutic Nutrition[67] be given to these
(Table 20).

TABLE 20. VITAMINS FOR HEPATIC COMA[67]

ORAL		PARENTERAL	
Thiamine HCl	2 mg.	Thiamine HCl	5
Riboflavin	2 mg.	Riboflavin	5
Niacinamide	20 mg.	Niacinamide	100
Ascorbic Acid	50 mg.	Calcium Pantothenate	20
Calcium Pantothenate	5 mg.	Pyridoxine	2
Pyridoxine HCl	0.5 mg.	Ascorbic Acid	300
Folic Acid	0.25 mg.	Folic Acid	1.5
Vitamin B_{12}	2 mcg.	Vitamin B_{12}	1
Vitamin A	5,000 units		
Vitamin D	400 units		
Vitamin K	2 mg.		

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* Mead Johnson and Company, Evans

ECIFIC THERAPEUTIC AGENTS

se. It has been the custom for many
give fairly large amounts of glucose
ally to patients with severe liver dis-
rticularly those with hepatic coma.
physicians, especially Jones,[28] have
ended it and have reported thera-
benefit from its use. There seems to
doubt that at least occasional pa-
vith hepatic coma may be benefited
e intravenous administration of glu-
his seems to be particularly true of
in whom the comatose state is some-
abile—that is, those patients who
spontaneous changes in the state of
usness. Because the spontaneous
s are so often present, it is difficult to
nt the true effectiveness of the glu-
ministration. The quantity of glucose
stered will depend upon the patient's
on, the intake of food by mouth or
h tube, and the fluid intake consid-
sirable (see p. 250). As high a con-
ion as 25 per cent glucose may be
the higher concentrations being given
to prevent local phlebothrombosis
e loss of glucose in the urine with
panying loss of water and dehydration.
basis for the therapeutic benefit that
may give may be administered cal-
a rapid source of easily available en-
r perhaps a stimulation of metabolic
ses. In connection with the latter it
en reported[78] that glucose stimulates
mbination of ammonia with glutamic
form glutamine, the latter presuma-
ting as a storehouse for ammonia and
ing it from the blood where it may
its toxic action. If a high ammonia
ntration is present and is contributing
comatose state (see p. 244), the ad-
ration of glucose in this circumstance
aid in its removal.

**renocorticotropic Hormone (ACTH)
ortisone.** It is too soon to evaluate the
f these hormones in the treatment of
ts with hepatic coma. Ducci[13] has re-
d 3 patients with viral hepatitis and
ic coma who responded to very large
(600 mg. per day) of cortisone. Sev-
ther patients have been seen who have
nded to similar amounts of the hor-
. Whether or not smaller doses will be effective is not known, and of particular importance is the fact that most patients who have been given either of these hormones in any dosage have shown no clinical change. In occasional instances patients with liver disease may even have been made worse.[9] It may be that these hormones are most effective in viral hepatitis and less so in coma associated with cirrhosis in chronic alcoholics. Further trial in suitable patients is certainly indicated.

Albumin. In patients with ascites and edema normal human serum albumin will sometimes induce a diuresis, but the dangers are thought by some to outweigh the advantages, the chief danger being a massive upper gastro-intestinal hemorrhage, usually from varices.[16] In hepatic coma albumin has been tried, generally without success, but occasional patients who have fallen into coma following bleeding episodes or following paracentesis have improved considerably following the administration of 25 or 50 Gm. of normal human serum albumin intravenously. The reason for the effectiveness of albumin when it does exist is unclear. Perhaps the lowered plasma volume after bleeding or paracentesis leads to oliguria which is relieved by the administration of albumin. This hypothesis should be investigated.

Glutamic Acid. Walshe has reported beneficial results in hepatic coma following the intravenous administration of 20 Gm. of glutamic acid (as sodium glutamate) and has suggested that the substance be given further therapeutic trial.[74] Were ammonia the toxic agent, glutamic acid might act by combining with the ammonia to form glutamine. In fact, glutamate has been shown to lower high blood ammonia content when present. However, a number of further observations do not give encouragement so far as the effectiveness of glutamic acid in the treatment of hepatic coma in chronic alcoholics is concerned.[77] Further study will be necessary to evaluate this therapeutic agent.

Antibiotics. The antibiotics including penicillin, chloramphenicol, streptomycin, chlortetracycline, oxytetracycline and related substances may be used in hepatic coma for the prevention and the treatment of acute specific infections or for possible specific therapeutic benefit on the comatose state itself. Their use in the treatment of specific infections is in no wise different from the treatment of infections in any other state. The appropriate antibiotic agent should be given in full therapeutic amounts. Diarrhea is frequent and is tolerated poorly in hepatic coma, so that antibiotics likely to induce it should be avoided when practicable.

The use of antibiotics in the specific treatment of hepatic coma is poorly documented and does not stand on firm ground. Only two of the antibiotics, chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), have been shown to have any specific therapeutic effect.[60, 17] In the case of both these drugs, occasional patients with hepatic coma exhibit a definite improvement in mental state. Some who have been deeply comatose have awakened and become quite conscious. In most instances, however, the effect has been short lived; the patient lapses into coma again, usually with a fatal outcome. In some the recurrent coma is heralded by massive gastro-intestinal bleeding or a staphylococcus diarrhea which ushers in the fatal termination. It is questionable whether more than transient therapeutic benefit has been achieved by the antibiotic treatment of hepatic coma. Moreover, the well-known fluctuations in the state of consciousness in these patients makes the assessment of the possible therapeutic benefits of these as well as other agents extremely difficult. Their use, therefore, is not recommended until furth knowledge has accrued.

If, in fact, chlortetracycline and oxytetra cyline do improve the state of consciousne in even a few patients, we must seek an e planation. None is too satisfactory. It ma be that these agents have some unknow intracellular action in either getting rid o intoxications or in some way stimulating ce lular metabolism. However, there is no ev dence that this is the case. An alternativ hypothesis would be that these two ant biotics act by reducing the intestinal flor thus decreasing the bacterial urease activit and in this way reducing the amount of am monia being absorbed from the gastro intestinal tract. Were it clear that ammon is the toxic agent, this might be an attractiv hypothesis. The difficulties in this interpreta tion may be seen in the discussion of an monia metabolism in the section on Patho genesis. Perhaps in addition to ammoni other substances such as amines are forme in the gastro-intestinal tract and are mo toxic than ammonia and that the antibiot acts by reducing the formation of both these nitrogenous compounds. This hypothe sis would help explain the recurrence coma after a few days in patients who im proved temporarily from the use of ant biotics, since the effect of the antibiotics o the organisms in the gastro-intestinal tract known to be short lived.

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Chapter 10

PATHOLOGY OF HEPATITIS

Hans Smetana, M.D.

INTRODUCTION

Nature of Viral Hepatitis. Epidemic hepatitis has been known since antiquity, but its differentiation from diseases of somewhat similar nature, such as leptospiral jaundice, toxic hepatitis and certain clinical types of obstructive jaundice, was indefinite. The rational pathologic interpretation of infectious hepatitis as the consequence of parenchymatous damage of the liver, rather than of obstruction of the biliary channels,[239] was made by Eppinger.[43] He also established the identity of acute yellow atrophy and infectious hepatitis as the fatal and the nonfatal variants of one and the same disease. This relationship had been suggested previously by several authors[8, 14, 22, 42, 52, 128, 190, 244] on the basis of clinical and epidemiologic data, but general acceptance of this point of view by the medical profession has been slow.

Types of Viral Hepatitis and Their Etiologic Agents. There is good circumstantial evidence for the assumption that hepatitis is caused by a virus, even though as yet the agent has not been seen, cultivated in vitro, or transmitted unequivocally to experimental animals or embryonated eggs. At least two forms of viral hepatitis are recognized: the naturally occurring type referred to as infectious hepatitis (catarrhal jaundice, infectious jaundice, etc.), and homologous serum hepatitis (transfusion jaundice, yellow fever vaccine jaundice, syringe jaundice, postarsphenamine jaundice, etc.) caused by incidental parenteral introduction of the virus, usually by means of blood or blood products.[82, 162, 176] Although the two infectious agents are perhaps related, they do not appear to be identical and do not impart cross immunity.[74, 82, 163] The latter point has been disputed,[175] but study of cases contributed to the Registry of Hepatic Pathology tends to confirm this view.

The properties of the causative virus are described as follows: It passes an L_2 Chamberland or Seitz EK filter, resists heating to 56° C. for 30 minutes, and is transmissible to man in serial passage by feeding or parenteral inoculation of infectious material. (For details see references.[20, 56, 75, 77, 89, 136, 165, 166, 168, 240]) The properties of the virus of homologous serum hepatitis are generally similar to those of the virus of infectious hepatitis.[12, 96, 137, 169, 175, 176, 180] Oliphant and Hollaender[177] reported inactivation of the virus of homologous serum jaundice by ultraviolet irradiation, but this method has proved to be unreliable. Inactivation of the virus of homologous serum hepatitis by means of heat has also been reported.[61]

There are arguments for and against the separation of the two diseases and their causative agents. Histopathologically, however, they produce identical hepatic lesions, and for the purposes of this discussion, infectious hepatitis and homologous serum hepatitis will be treated as a single disease. Whenever the type is known it will be identified, but the term "viral hepatitis" will be used to designate hepatitis due to either etiologic agent.

INFECTIOUS HEPATITIS

Incidence and History

The frequency of spontaneously occurring hepatitis varies in different parts of the world,[14, 78, 93, 108, 124, 168, 240] and it is endemic in certain areas.[28, 32, 36, 60, 94, 103, 151, 152, 205, 210, 223, 236, 237, 251, 252] The epidemic form is associated ordinarily with disasters and the massing of human beings in close quarters. It is one of the scourges of war.[4, 20, 25, 26, 28, 32, 35, 36, 38, 41, 45, 53, 54, 58, 60, 66, 67, 76, 86, 90, 92, 93, 101, 102, 112, 116, 121, 126, 129, 149, 151, 153, 159, 170, 173, 179, 205, 210, 214, 222, 223, 229, 235, 243, 251, 252, 253, 254] On the other hand, sporadic cases may spring up without warning, even when there is no crowding.[67, 97, 130, 152, 184, 209] Despite various designations, the clinical symptoms described in both past and recent epidemics seem to be essentially identical.

Epidemic hepatitis was recognized in antiquity. In the Western world, one of the earliest comprehensive descriptions of the disease was recorded during the eighth century, in a letter from Pope St. Zacharias,[59] to St. Boniface, Archbishop of Mainz. During the wars of the Middle Ages, as an epidemic disease, it was overshadowed only by plague and cholera. It flourished during the Napoleonic wars when it was first referred to as "epidemic jaundice" by Mende.[155] The reports by Smart[215] and Woodward[254] of jaundice occurring in United States troops in the Civil War emphasized its importance during these campaigns. During World War I, armies in many parts of the world suffered from the effects of such epidemics, and no part of the front was exempted.[17, 101, 141, 149, 205, 251, 252] Although the United States soldiers suffered perhaps least, epidemics broke out later among occupation armies in Germany. Wallgren[244] has written an excellent report and review of the severe epidemic that occurred in the Scandinavian countries at this time. In the United States a large group of postwar cases was reported by Michie.[158] Again during and after World War II, epidemics of varying intensity occurred notably in the United States, Germany, France, Greece, Russia, the Near East and Japan.[20, 28, 32, 35, 36, 59, 60, 66, 92, 116, 151, 179, 210, 214, 223, 254] The Korean conflict proved to be no exception, according to the report of Deschamps and Steer,[31] but fortunately the character of this outbreak was rather mild.

The extent and the pattern of epidemics may be influenced by local factors, by the arrival of newcomers susceptible to infection,[59] or by the movement of troops carrying the agent into new territory.[121] Comparison of the attack rates in the civilian population and in troops have been made by McFarlan.[151] Variations in the pathogenicity and the infectiveness of the virus, environmental conditions and the degree of the acquired immunity of the population are factors responsible for variations in the incidence and the severity of the disease.[60, 63]

EPIDEMIOLOGIC DATA

Spontaneous infectious hepatitis appears to be propagated by person-to-person contact, the virus probably gaining entrance through the gastro-intestinal tract, although the nasopharyngeal route cannot be ignored entirely. Outbreaks, presumably due to the contamination of water[60, 107, 165, 174] or milk[160] and other foods,[191] have been described also.

MORTALITY AND MORBIDITY

With the exception of occasional epidemics, the mortality rate has been low; the morbidity always has been high. Complete and reliable statistical surveys are difficult to obtain during wartime because of security restrictions. During the first year of the Civil War, 10,929 cases of infectious hepatitis occurred in the Northern Armies, with 40 fatalities. The incidence of morbidity varied from 3.4 per cent in the Armies in Missouri to 8 per cent in Grant's eastern army. On the other hand, Smart[215] reported 243 fatal cases among Union troops in the entire war, but figures of the morbidity rate are inadequate for comparison. During the epidemics among U. S. troops in 1942, the mortality rate varied in different areas from 0.2 to 0.4 per cent. The morbidity rate was not reported.

IMMUNITY

An attack of viral hepatitis usually confers immunity to the specific virus causing the disease, although the degree of immunity may vary in individual cases. Lack of development of protective antibodies is suggested in protracted cases in which the body appears to be incapable of overcoming the infection within a reasonable period of time. Such instances suggest that an uncertain equilibrium between the liver cells and the virus has been reached, a situation somewhat analogous to that observed in some cases of persistent herpes infection of the oral mucosa[117] or herpes encephalitis.[142] By means of judicious administration of normal human gamma globulin it has been possible to confer passive protection against infectious hepatitis[62, 87, 226] and homologous serum hepatitis.[39, 65]

Since only a portion of the population is affected during epidemics of infectious hepatitis, it is believed that many individuals possess either a natural resistance or an immunity acquired by a previous, mild, undiagnosed attack of the disease. This probably also accounts for the fact that only sporadic cases occur in periods following large epidemics in widely separated parts of the world. That there is a comparatively constant number of cases of viral hepatitis between epidemics may be attributed to homologous serum hepatitis.[83, 183, 184]

SEASONAL AND REGIONAL DISTRIBUTION

Infectious hepatitis has been reported from all parts of the world and every climate. Outbreaks may occur at any time during the year, but the highest incidence of single cases and the peak of epidemics usually coincide with autumn and early winter months. As previously mentioned, crowding, especially if poor sanitary conditions exist, may play a role in the colder months of the year.

AGE OF PATIENT

Infectious hepatitis is primarily a disease of children and young adults but may occur at any age. Wickström[250] maintains that this "index of contagiousness," while variable, is greatest between the ages of 6 and 20, with the peak below the age of 10. In the Armed Forces the young adult is particularly subject to the disease. In general, persons up to the age of 30 are most susceptible,[60, 151] with a sharp decline in the attack rate above this age.[60, 121]

HOMOLOGOUS SERUM HEPATITIS

DEFINITION

Hepatitis of this type is indistinguishable clinically and pathologically from infectious hepatitis, except for the longer incubation period.[6] It is caused by the parenteral transmission of the agent from contaminated blood or blood products,[82, 109, 176] or by surgical, dental or other instruments.[83, 125, 198]

HISTORICAL NOTES

Several severe epidemics of homologous serum jaundice have been caused by certain disease-preventive procedures despite the clear descriptions of preceding similar outbreaks and their causes. The first known episode of this kind occurred in Bremen, Germany, in 1885, when 1,289 workmen were inoculated against smallpox with vaccine prepared from human lymph. Of this number, 199 came down with hepatitis, while another group of 500, vaccinated with a different lymph at the same time, remained well.[135] Other outbreaks of hepatitis following immunization against yellow fever with vaccine prepared from human serum were described by Findlay and MacCallum[46, 47] and Findlay, MacCallum and Murgatroyd[49] in 1937, by Soper and Smith[221] in 1938, by Fox et al.[55] in 1942, and Findlay and Martin[48] in 1943. Several similar mishaps are recorded.[83, 176, 227] Although Findlay and his group[46, 47, 49] had suggested that a filtrable etiologic agent derived from the human serum used to prepare the vaccine was the cause of the infection, thousands of cases of homologous serum hepatitis were produced by the administration of icterogenic yellow fever vaccine to U. S. Army personnel in 1942.[48, 106, 206, 232, 233]

IMMUNOLOGIC AND EPIDEMIOLOGIC DATA

Accidental transmission of the virus of homologous serum hepatitis with blood plasma or serum harboring the agent is in all likelihood responsible for the sporadic episodes in the hospitals and in battle areas.[65, 96, 197, 204, 208] In addition, it is now recognized as the cause of hepatitis following treatment of syphilis with arsenicals[201, 202, 203, 227] or other types of antisyphilitic drugs,[125, 198] as well as that occurring after withdrawal of blood for various purposes and procedures.[83, 156] The long incubation period in homologous serum hepatitis makes it difficult for the patient to recollect minor procedures in the past which might have been responsible for the transmission of the disease (dental treatment, manicures, etc.). The possible contamination of plasma with hepatitis virus presents a great problem in the management of blood banks[208] and it is one of the important factors in the search for a sterile and reliable plasma expander.

EXPERIMENTAL TRANSMISSION OF VIRAL HEPATITIS

Transmission to Experimental Animals

Transmission of the clinically evident disease to experimental animals has generally failed. There are, however, a number of reports which merit consideration. Andersen and Tulinius[3] described experiments in transmission of spontaneous porcine hepatitis by feeding liver of infected animals to pigs on a deficient diet; by feeding duodenal juice of patients suffering from hepatitis to pigs; by intravenous injection of blood from human beings to animals; and by inoculation of infective material into embryonated eggs. Attempts to confirm these observations have not been successful.[16, 44, 88, 98, 236] In particular, Findlay, MacCallum and Murgatroyd[49] could not duplicate the results of Andersen and Tulinius[3] and reported negative results of attempted transmission by various methods to a variety of animals, including monkeys, hedgehogs, ducks, cats, ferrets, rabbits, guinea pigs, field moles, rats, fowl, mice and pigeons, which were kept under observation for many months; inoculation into embryonated eggs also proved to be unsatisfactory. Negative or inconclusive results were also reported by Cameron,[20] MacCallum and Miles,[139] Benda, et al.[13] and Verlinde and Boer.[238] Transmission experiments using insect vectors (ticks, flies, bedbugs) on human beings were also unsuccessful. Attempts to transmit homologous serum hepatitis to horses by inoculation of yellow fever vaccine, icterogenic to man, were also futile.[110]

Jordan and Mirick,[111] repeating the experiments of MacCallum and Miles,[139] reported development of ascites and alterations in the liver of inoculated mice. Hanger et al.[69] also reported lesions in the liver and spleen of rats infected with serum from patients with hepatitis.

The histologic changes in the liver reported by Jordan and Mirick,[111] Hanger, et al.,[69] and others, do not seem to be comparable with those seen in human viral hepatitis. It is possible, however, that changes produced in experimental animals are not identical with those seen in man; on the other hand, accidental transmission of an agent other than that of human hepatitis may have occurred.

In relation to experiments with mice, the report by Olitsky and Casals[178] of spontaneous lesions in the liver of stock albino mice is of importance.

Russian investigators[213] have reported successful transmission of Botkin's disease (infectious hepatitis) to guinea pigs by feeding gastric contents from patients with hepatitis. Also, it was reported that the disease had been transmitted by contact to guinea pigs which, though not given infectious materials, were placed in the same cages as the experimental animals.

The described isolation of strains of the causative agent of human infectious hepatitis by Hara et al.,[70] its demonstration by means of the electron microscope,[70, 71] and successful passages through generations of mice,[71] as well as the preparation of an antigen for a specific dermal reaction for epidemic hepatitis,[72] must await confirmation. Bang and Gay[10] are trying, by tissue culture methods, to develop cells susceptible to destruction by the virus of infectious hepatitis.

Transmission to Human Volunteers

The first successful demonstration of the infectivity of duodenal contents and blood in human volunteers by Voegt[240] has been amply confirmed by several investigators,[20, 50, 56, 75, 77, 79, 81, 89, 138, 163, 165] and the experiments have been extended to parenteral routes[20, 56, 75, 77, 79, 81, 89, 138, 163, 175, 240] including the nasopharynx.[77, 85, 138, 163, 165] The period of infectivity has been found experimentally to extend from 3 days before to 8 days after the appearance of jaundice.[83] Attempts to prove infectivity in cases of apparent persistent hepatitis were unsuccessful.[100]

Transmission experiments on volunteers brought positive results when the agent of homologous serum hepatitis was introduced by the parenteral routes[48, 77, 80, 83, 90, 139, 140, 166, 171, 179] in serial passage[163, 167] causing development of immunity to this type of virus, but apparently they were unsuccessful when the oral and the nasopharyngeal portals of entry were used.

Virus has been demonstrated in the blood of volunteers during the incubation period 87 days,[169] 60 days,[180] and 16 days,[80] before the appearance of jaundice but not during convalescence.[48, 80, 176, 180] The presence of virus in the urine of patients suffering from infectious hepatitis has been both asserted[50, 233, 240] and denied.[77, 138, 165] No vector has as yet been identified, although the possibility of transfer of hepatitis by insect bite has been considered.[118, 235]

PATHOLOGY OF VIRAL HEPATITIS

Review of More Recent Reports

The pathology of the fatal variety has been documented exhaustively by Lucké[131] and Lucké and Mallory,[133] confirming and enlarging previous studies and observations.[91, 119, 120, 145, 154, 194, 196, 242, 256, 257] Lucké[132] also studied cases with a past history of viral hepatitis and reported complete recovery in cases in which subsequent death was accidental. The boundaries of the possible consequences of viral hepatitis from the fulminant fatal type to the complete restitution of the liver after an attack of nonfatal hepatitis are presented in this series of articles.

Reports of studies of various phases of viral hepatitis by means of needle biopsies[5, 34, 105, 122, 195] or by peritoneoscopy[146] have formed the basis for the dynamic interpretation of the successive histopathologic changes which take place in the liver during the disease. Although aspiration biopsy of the liver was slow to be accepted as a diagnostic procedure in the continental United States, interest in studies based particularly on the correlation between results of liver function tests and of aspiration biopsies has since developed to a high degree.[157, 185, 186, 187, 188, 224]

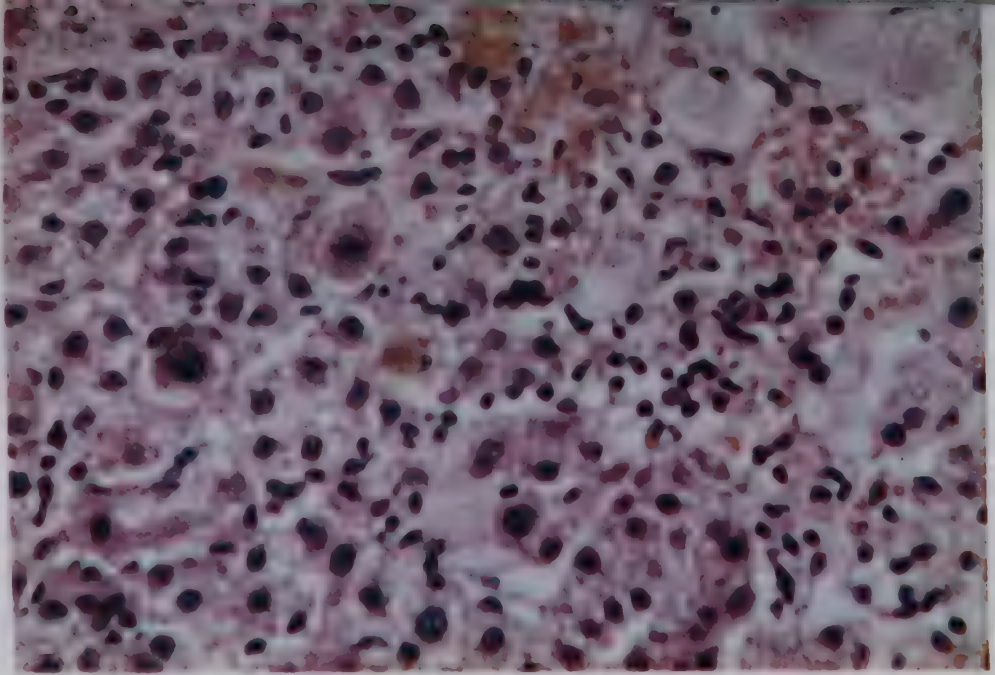
Materials and Methods

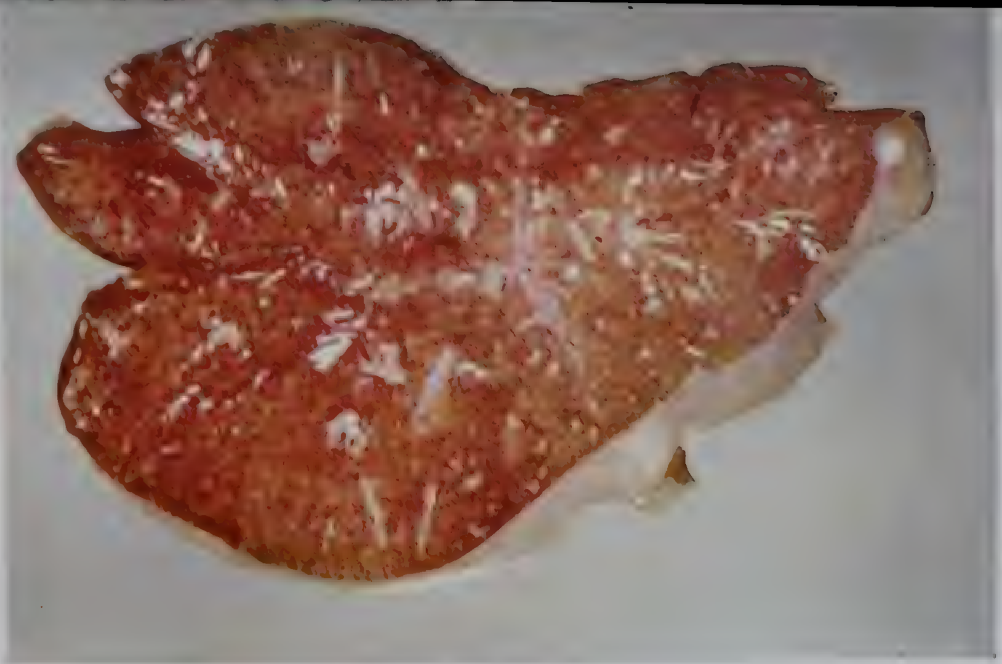
The material for the present study of the histopathology of viral hepatitis was furnished by the cases in the Registry of Hepatic Pathology at the Armed Forces Institute of Pathology. The diagnosis of infectious hepatitis is recorded in 979 of 5,036 cases studied by needle biopsy and entered in the Registry of Hepatic Pathology as of March, 19 This constitutes 20 per cent of the total ca in comparison with 10 per cent portal c rhosis, 9 per cent portal fibrosis of uncert etiology, 3 per cent cirrhosis other than p tal and 10 per cent hepatic disease show fatty metamorphosis. Normal or minim histologic changes of undiagnosed cau possibly residues of hepatitis, were recor in 18 per cent.

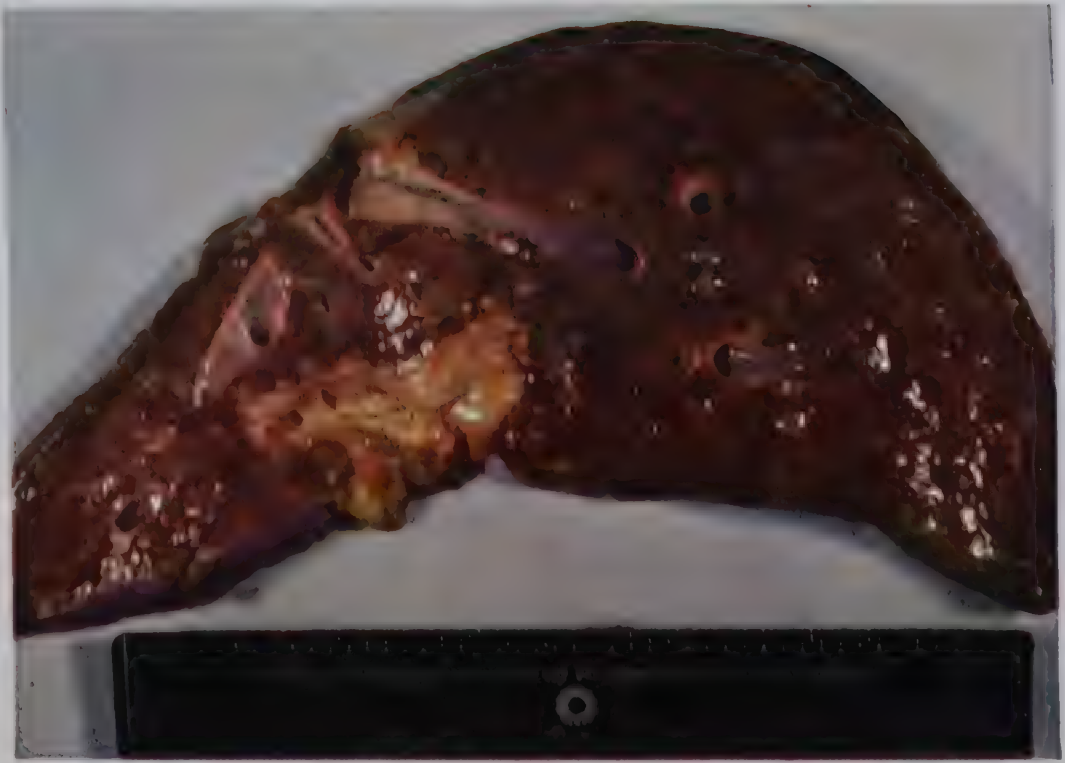
Histogenesis of Viral Hepatitis

The basic and characteristic patholog sion of acute viral hepatitis is the damage the individual liver cells leading to th degeneration or necrosis. There is reason assume that the entire organ is affected, e though the final results indicate that cert portions of the liver appear to have s tained more severe damage than others. basis for this assumption is the similar h tologic appearance of needle biopsies tained from different parts of the liver du laparotomy and the comparable appeara of the liver tissue in serial needle biop taken at random. The histopathol changes that follow the original injury r resent the result of an interaction betw the infective agent as it overcomes the ural resistance and the reaction of local general body defenses as they attemp combat the assault. At the same time mechanism for removing the debris necrotic cells is put into motion, and placement of damaged cells by regenera takes place. Individual cells cannot be paired without disruptive effects on the f tion, as well as the functional structure the organ. The results of the profound function of the cells are expressed in outcome of liver-function tests; the dis tion of the biliary capillaries secondar necrosis of individual liver cells which their walls is an expression of damage t functional structure of the liver and pe bile to enter the blood stream. The jau which constitutes an integral clinical m festation of the disease is a corollary t disruptive change.

The consequences of hepatitis are g ally proportional to the extent of the da to the parenchyma. A single, mild a with necrosis of some of the liver cell





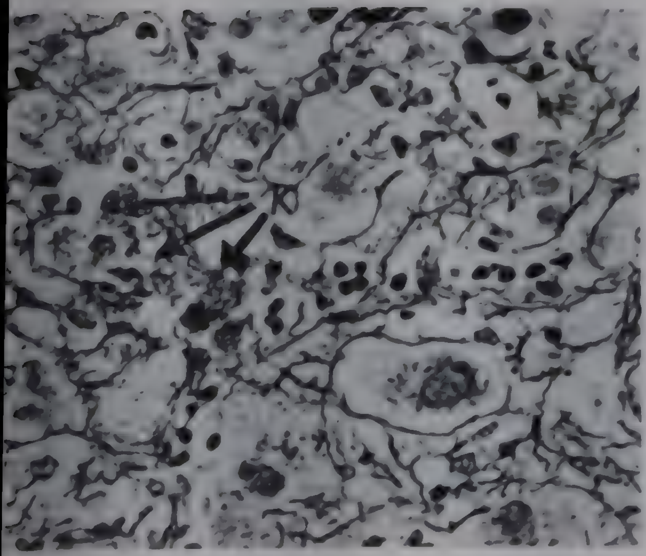


(A, *Top, left*) Acute nonfatal homologous serum hepatitis. Needle biopsy of liver 3 days after onset of jaundice. There is striking alteration of liver cells with formation of balloon cells and acidophilic bodies. The distortion of architecture is due to the irregularity of liver cells forming the columns. Monocytic infiltrates in the sinusoids. Golden-yellow lipofuscin Kupffer cells. Focal congestion of sinusoids. × 325. (AFIP Acc. 325047)

(B, *Top, right*) Acute fatal infectious hepatitis with death 10 days after onset of disease. Liver: 1,225 Gm., soft in consistency. Cross section, showing the peculiar orange-yellow and ochre-yellow tinge of the hepatic parenchyma. The centers of the lobules are congested. × 1/3.2. (AFIP Acc. 279426)

(*C, Bottom*) Acute fatal infectious hepatitis. Death 2 weeks after onset of illness. Liver: 660 Gm., yellow brown in color and soft in consistency. Cross section of liver, showing numerous ochre-yellow and brownish-yellow sharply circumscribed nodules representing regenerating liver tissue in collapsed stroma and congested sinuses. × 1/2.5. (AFIP Acc. 170637)

PLATE 1



G. 81. Acute nonfatal homologous n hepatitis. Needle biopsy of liver lays after onset of jaundice. Conation of reticulum fibers in areas of osis of liver cells; argentophilic lipon in liver cells and Kupffer cells at Wilder reticulum stain. × 470. ned Forces Institute of Pathology, 325047)

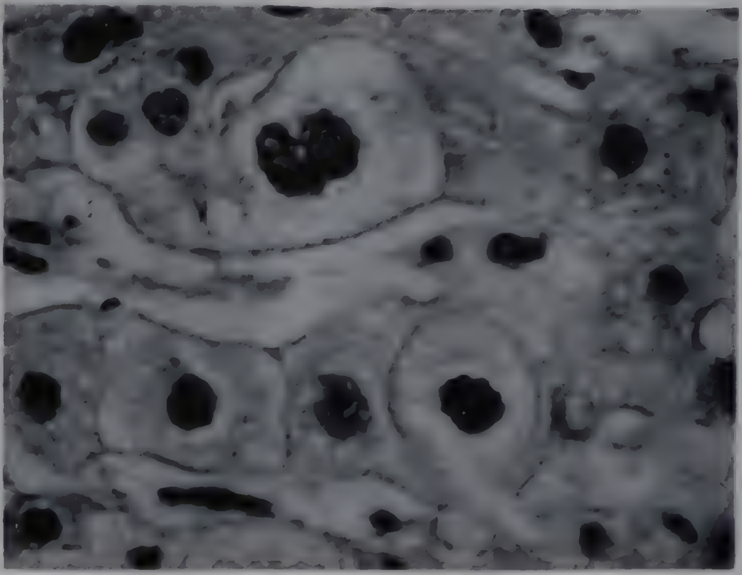


FIG. 82. Acute nonfatal homologous serum hepatitis. Needle biopsy of liver 5 days after onset of hepatitis, 2 days after onset of jaundice. Marked ballooning of liver cells, some binucleated, and mitotic figures of nuclei in some liver cells. × 900. (Armed Forces Institute of Pathology, Acc. 316131)

by undisturbed regeneration and res- of the cellular and lobular archi-, characterizes a transient type of is, usually followed by complete heal- d restitution of normal function. Si- eous destruction of all or most of the lls, accompanied by profound altera- f the structural elements, must, of ty, cause cessation of the function of gan thereby leading to early death. n these two extremes lie most in- of uncomplicated infectious hepatitis. ent hepatitis and postnecrotic condi- epresent deviations from the standard l picture which are reflected in their tive histopathologic alterations. In ad- atypical forms of infectious hepatitis mplications which may alter the clini- irse result in histopathologic pictures ng from that in standard cases of ous hepatitis.

OPATHOLOGY OF ACUTE NONFATAL VIRAL HEPATITIS

topathologically, the acute phase of epatitis is characterized by the effect rying degrees of damage, including is, of many of the liver cells, with tion of liver cell cords and plates, interruption of the continuity of bile canaliculi and collapse of the sinusoids (Plate 1). The complete disintegration and disappearance of severely affected liver cells are a common, though remarkable feature; even in the earliest phases observed, stages of transition from necrosis to disappearance of the debris are rarely seen, but cytoplasm and nuclei vanish without trace as though they had dissolved or exploded into fine particles. The former site of such vanished cells can be recognized only by the distortion of the architecture of the cell columns, by the presence of mononuclear reactive cell elements, and by the accumulation of lipofuscin[18, 114, 131, 216, 217, 218, 248] set free during the destruction of the liver cells and then phagocytized by adjacent Kupffer cells (Plate 1). This pigment is not granular bilirubin, as suggested by Axenfeld and Brass.[5] It can be demonstrated with fat stains and is partially acid-fast, as well as argentophilic (Fig. 81). It resists bleaching, is not doubly refractive under the polarizing microscope and does not stain for iron. According to Hamperl[68, 246] it represents ceroid. The origin of the mononuclear wandering cells forming the intralobular infiltrates about areas of necrosis of liver cells is somewhat uncertain, although most proba-

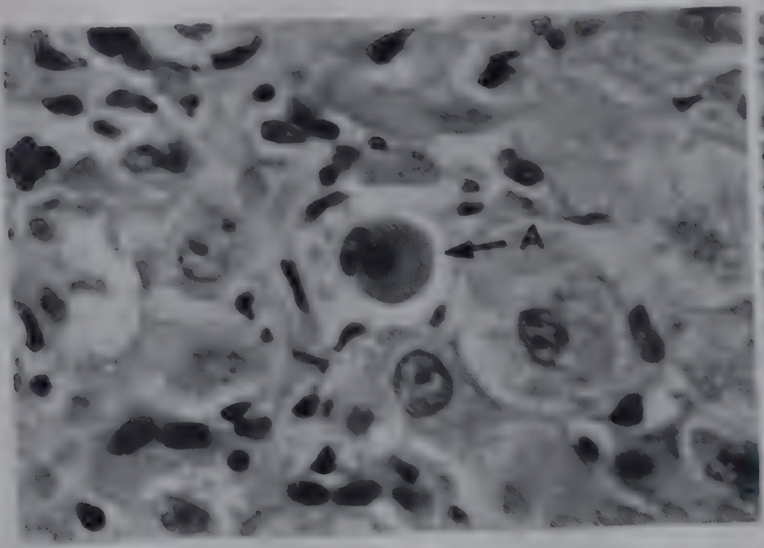


FIG. 83. Acute nonfatal homologous serum hepatitis. Needle biopsy of liver 4 days after onset of hepatitis and 2 days after onset of jaundice. Striking irregularity of liver cells with formation of binucleated elements and balloon cells. Acidophilic body in sinusoids at "A." × 900. (Armed Forces Institute of Pathology, Acc. 318055)

bly it is reticuloendothelial, as Axenfeld and Brass[5] state. Even during the earliest phases of hepatitis the portal canals contain infiltrates, composed chiefly of monocytes in addition to plasma cells, lymphocytes and eosinophils, although the intralobular changes may be slight. It is uncertain

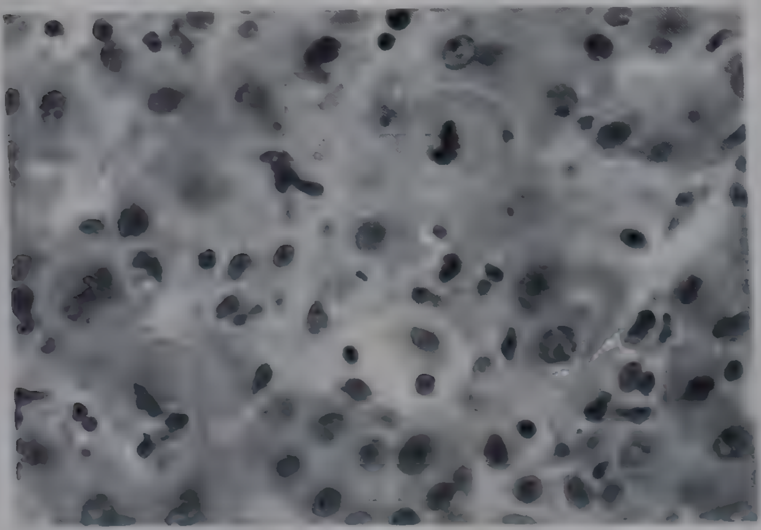


FIG. 84. Acute nonfatal infectious hepatitis. Regeneration of liver cells. Needle biopsy of liver 23 days after onset of hepatitis, 15 days after onset of jaundice. Marked irregularity of liver cells, some binucleated, others showing mitotic figures. Scanty infiltrates of monocytes in sinusoids. × 600. (Armed Forces Institute of Pathology, Acc. 313709)

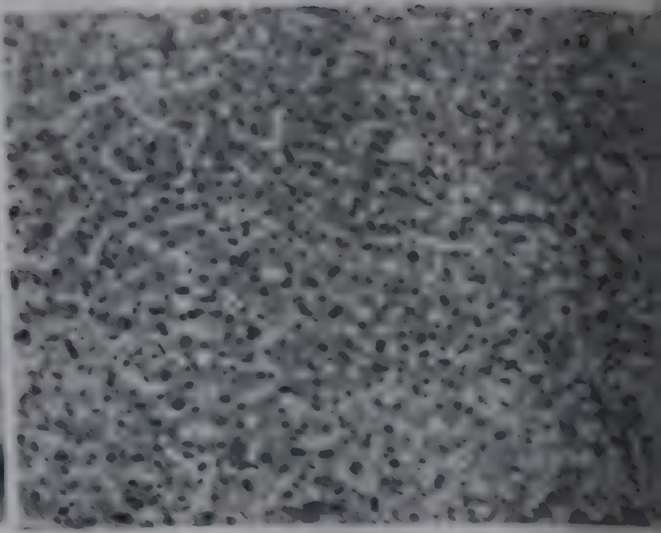
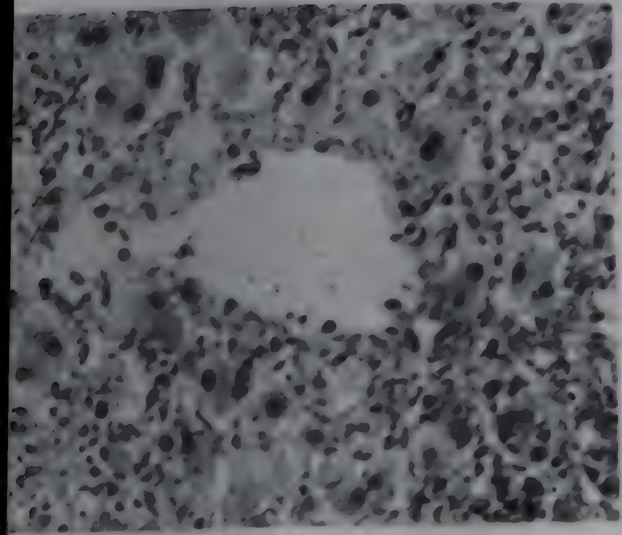


FIG. 85. Effect of chlortetracyc
(Aureomycin) treatment on liver. Ne
biopsy of liver 1 month after onse
infectious hepatitis, extensively tre
with chlortetracycline. Subsiding hepa
with moderate fatty metamorphosis
liver. Scanty monocytic infiltrates
sinusoids. Slight irregularity of liver
with occasional binucleated forms. ×
(Armed Forces Institute of Pathol
Acc. 284515)

whether these reactive cells have reac
portal canals by way of portal ves
have originated from local reticuloen
lial elements. The eosinophilic leu
appear to be mature cells and are
expression of peripheral blood eosin

Side by side with necrosis of in
liver cells are degenerative alterat
individual liver cells, characterized e
a balloonlike swelling or by hyali
with shrinkage of the cytoplasm. T
uolization is neither due to fat nor t
gen and probably indicates a re
change, because the nuclei of such
still capable of mitosis (Fig. 8
hyalinization and the shrinkage of liv
on the other hand, appear to rep
more profound damage, leading to
mation of "acidophilic bodies,"
constitute one of the characteris
marks of infectious hepatitis (Pla
Fig. 83).

Replacement of damaged and
liver cells is accomplished by mi
amitotic regeneration, which sets
immediately following the injury (
It is recognized by a varying n



86. Acute nonfatal homologous
hepatitis. Needle biopsy of liver
after onset of jaundice. Monocytic
te in sinusoids. Binucleated liver
nd "balloon" cells about efferent
× 275. (Armed Forces Institute of
ogy, Acc. 325047)

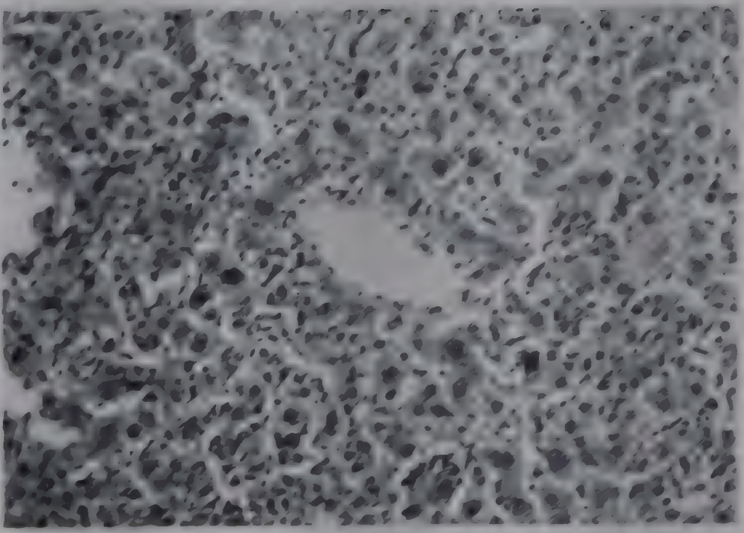


FIG. 87. Acute nonfatal homologous serum hepatitis. Needle biopsy of liver 26 days after onset of hepatitis and 25 days after onset of jaundice. Liver cells about efferent veins, showing slight irregularities and occasionally containing 2 nuclei. Small focal monocytic infiltrates in sinusoids. × 160. (Armed Forces Institute of Pathology, Acc. 327042)

of nuclei of liver cells which have
injury, and by the presence of nu-
inucleated and multinucleated cells,
arger than their quiescent neighbors.
ll formation does occur but is
prominent nor a characteristic fea-
tty metamorphosis is generally ab-
ty metamorphosis of even slight de-
aks against liver injury due to in-
hepatitis, except in instances where
had been on a special dietary regi-
had been treated vigorously with
cs or hormones (Fig. 85). Histo-
dence of stasis of bile in bile cana-
also not a feature during the early
of acute nonfatal hepatitis except
cases, although clinical jaundice
s present at this stage.

amage to liver cells is seldom limited
articular part of the lobule, and the
lobular architecture is not disturbed
; the efferent veins are seen in their
ntral location; and the portal canals
rged and prominent; the radial ar-
nt of the parenchymal cell columns
rved, but frequently their contour is
d by the effect of damage and drop-
t of individual liver cells or groups
; the reticulum fibers are preserved
be collapsed and condensed in areas
osis of liver cells (Fig. 81). The portal and hepatic vessels are essentially unaltered, as are the bile ducts in the portal canals. However, in some cases the cells about the efferent veins may exhibit especially severe damage (Fig. 86) while in others they appear to be practically unaffected (Fig. 87).

The cause of all these changes can be reduced to the simple equation of damage and necrosis of liver cells, cellular inflammatory reaction and cell regeneration, occurring side by side. In our experience no portion of the lobule is particularly favored, and none appears to be wholly exempt.[5] The entire organ is generally affected in the same fashion, with little variation in character and intensity throughout the parenchyma.[18, 246] Intranuclear or cytoplasmic inclusion bodies have not been found in liver cells, Kupffer cells, or lining cells of bile ducts in viral hepatitis.[18]

The hyaline cytoplasmic inclusions in the liver cells, described by Thaler[230, 231] in infectious hepatitis and yellow fever, are probably early stages of hyalinization of damaged liver cells and precursors of "acidophilic bodies." Their histologic character does not convincingly suggest true viral inclusion bodies, even though it cannot be denied that they might result from cytoplasmic damage by a virus. Inclusions in liver cells in instances of icterogenic hepatitis also have been described by Nicolau.[171] Interesting observations of alterations of nuclei, nucleoli and of the cytoplasm of liver cells in viral hepatitis, when studied with the electron microscope, have been made recently by Bang.[9]

The histopathologic phenomena encountered in acute viral hepatitis indicate that the damage is directed primarily to liver cells and is presumably the action of a specific virus which seems to interfere with the very vital functions and the continuity of the parenchymal cells. The exact fashion in which the virus attacks the cells and alters their components is as yet unknown, but enzymatic action or interference is suspected.

The liberation of lipofuscin from necrotic liver cells with subsequent phagocytosis by Kupffer cells is not limited to infectious hepatitis, for it may be noted in instances of toxic damage of liver parenchyma, particularly that due to carbon tetrachloride. Since lipofuscin is not normally found in Kupffer cells, its presence in these cells, in conjunction with other features, can be interpreted as presumptive evidence of necrosis of parenchymal cells.

The histogenesis of acidophilic bodies is pictured as follows: There is condensation of the cytoplasm with apparent detachment from the cell membrane (Plate 1 and Fig. 83). At the same time the nucleus becomes pyknotic and sometimes shows karyorrhexis. The homogenized and strikingly acidophilic cytoplasm becomes rounded off. Often this body appears to lie free in tissue spaces; at other times it is found phagocytized by Kupffer cells (Fig. 83); in most instances it is extruded eventually into the sinusoids. Although the pathogenesis of the acidophilic body is not known, in all probability it is the result of injury to an individual cell with coagulation necrosis of the cytoplasm.

Acidophilic bodies similar to those occurring in infectious hepatitis are seen also in the liver in toxic hepatitis, burns, chronic passive congestion, and in cases of liver damage due to tannic acid; occasionally, they are found also in instances of obstructive jaundice and after treatment with n gen mustard. However, the findings of s bodies, despite their lack of specificity combination with other histopathologic tures, adds assurance to the diagnosis of v hepatitis.

The presence of wandering cells wi the tissues of the lobules is also interpr as an indication of reaction to injury. W their presence in the portal canals is pro bly secondary to migration from portal sels, intralobular infiltrations seem to o nate locally from reticuloendothelial c There is no evidence that the infiltrate the portal triads can be attributed to prin injury of the periportal tissues.

Although none of the above-mentio individual features are specific, it is the ied combinations in which they occur the kaleidoscopic transformations of the ally quiescent picture of the normal lobule that are highly characteristic of acute phase of nonfatal hepatitis. T alterations are such regular features of condition that they can be considere pathognomonic and highly diagnostic.

The reliability of liver-function tes an index of quantitative damage of tissue is difficult to evaluate becaus cellular changes in hepatitis are of so types and degrees of severity. Howeve results of some serve as relative mea of changes which take place in the during the course of this disease.

Although a certain relationship be the clinical stage of infectious hepatiti the outcome of laboratory tests exists.[3 161, 164, 185, 187, 188] such a pattern may b cult to apply in the interpretation isolated case of infectious hepatitis. In tion, it has been stated that some liver-function tests in use do not actua the function of the liver.[21] As yet no s laboratory test for the diagnosis of tious hepatitis has been devised and sults of some of the tests in use are th in a number of diseases of the liver.[57 In cases of possible extrahepatic bili struction, the lack of such a test is a handicap when surgical intervention i considered. In such instances hi study of aspirated liver tissue usua decide the issue. Until reliable speci

TABLE 21. CLINICAL AND LABORATORY DATA AT TIME OF LIVER BIOPSY IN 20 CASES OF ACUTE NONFATAL HEPATITIS

CASE No.	AFIP ACC.				BIOPSY, DAYS AFTER		CEPHALIN FLOCCULATION	THYMOL TURBIDITY UNITS	SERUM CHOLINESTERASE (ΔpH/HR)	SERUM ALKALINE PHOSPHATASE†	URINE BILIRUBIN	SERUM BILIRUBIN MG./100 CC.			
		Age	*Race*	*Sex*	*Symptoms*	*Jaundice*						*One Minute*	*Total*	*Highest Recorded Level*	*Returned to Normal* (Days)
1	308670	20	C	M	4	2	2+	6.8	Not det.	9.7	3+	2.6	3.5	5.6	23
*2	309299	18	W	M	12	1	4+	4.5	Not det.	14.2	2+	6.9	11.1	11.1	24
*3	313709	25	W	F	9	2	3+	6.8	Not det.	12.7	4+	7.6	11.8	12.7	60
*4	316131	28	W	M	5	2	Neg.	4	0.9	21.1	2+	7	9.4	23	78
5	316612	19	W	M	6	4	2+	4	0.5	22.5	3+	8.4	13.3	15.2	30
6	317181	31	C	F	4	4	4+	6.6	0.6	10.2	3+	11.4	16.1	16.1	46
7	318055	19	W	M	3	2	Neg.	2	0.7	7.3	2+	2.9	4.6	5.9	40
8	319038	36	W	M	9	4	4+	7	0.5	11.3	4+	9.7	14.6	15.6	54
9	319263	33	W	M	11	6	4+	8.1	0.5	11.5	3+	12	18.5	21	60
10	319658	18	W	M	6	6	2+	3	0.7	12.1	Neg.	1.8	2.9	2.9	10
11	319817	20	W	M	9	6	4+	8.1	0.4	11.4	2+	6.8	11.7	11.7	50
12	319818	22	W	M	4	1	3+	5.7	0.5	10.5	4+	3.4	6.4	6.4	50
13	320643	21	W	M	9	6	4+	8.1	0.6	9.9	3+	6.4	9.6	9.6	33
14	320738	20	W	M	8	5	3+	9.8	0.7	14.1	1+	5.4	9.6	9.6	30
15	322713	20	W	M	4	1	3+	5.4	0.68	7.1	1+	2.9	5.0	17.0	41
16	323372	19	W	M	8	5	2+	2.9	0.88	6.4	Not det.	5.8	8.5	8.5	31
17	325047	20	W	M	3	2	Neg.	2.9	0.46	7.2	Neg.	2.9	5.6	5.6	18
18	327042	21	W	M	6	4	4+	6.8	0.56	Not det.	Not det.	5.8	9.6	9.6	40
*19	328072	34	W	M	11	4	4+	7.9	0.39	9.8	4+	12.2	18.0	21.2	60
*20	327109	19	W	M	9	2	4+	5.0	0.59	9.3	3+	3.9	6.5	8.2	22

* Did not receive either blood or plasma.

† Modified Bodansky units. (Shinowara, G. Y., et al., J. Biol. Chem. **142**:921, 1942)

(From Keller, T. C., Giges, B., and Smetana, H. F.: Histopathologic study of acute nonfatal hepatitis, Mil. Surgeon **109**:425, 1951)

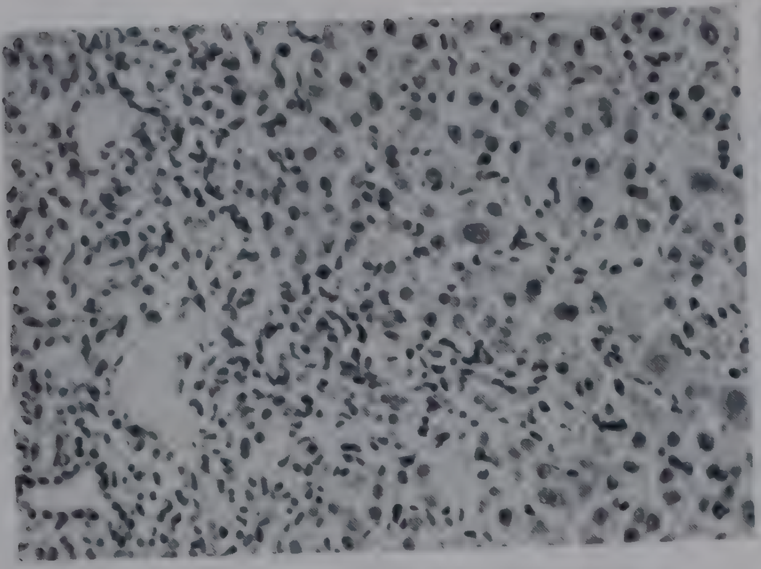


FIG. 88. Acute nonfatal homologous serum hepatitis. First needle biopsy of liver 8 days after onset of hepatitis, 4 days after onset of jaundice. Marked irregularities and degenerative changes of liver cells, numerous focal necroses and portal infiltrates composed of monocytes and eosinophils. × 300. (Armed Forces Institute of Pathology, Acc. 329833)

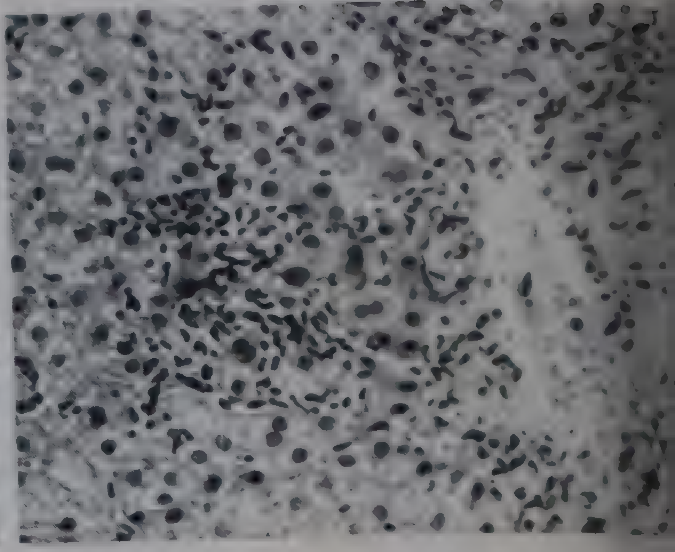


FIG. 89. Acute nonfatal homologou serum hepatitis, subsiding. Second need biopsy of liver 38 days after onset hepatitis. The cellular pattern of the liv parenchyma is fairly regular except for few multinucleated liver cells. Portal i filtrates are diminished, but occasion focal necroses are present in lobule × 300. (Armed Forces Institute of P thology, Acc. 329833)

are available, the histopathologic appearance of the liver tissue is considered as the only single method for unequivocal diagnosis of acute nonfatal hepatitis.

Results of routine laboratory tests, made at the time that needle biopsy of the liver was performed on 20 patients with acute nonfatal hepatitis, are presented in Table 21.

HISTOPATHOLOGY OF SUBSIDING NONFATAL VIRAL HEPATITIS

A great majority of patients with infectious hepatitis survive the original attack and eventually recover,[132] thereby acquiring a permanent immunity[66, 83, 244] to the type of virus which caused the disease. The length of time necessary for recovery is roughly proportional to the amount of injury produced and the duration of the active progressive disease. Clinically, cases of subsiding hepatitis are characterized by diminishing signs and symptoms of hepatic disease and by decreasing jaundice; the results of laboratory tests tend to return to normal values. If the disease is actually overcome, it is only a matter of time until the damaged necrotic liver cells are replaced by regenerated cells, and the disrupted plates, the bile cana and the sinusoids are repaired so that mal physiologic function can be resu

Histologically, this stage is recogniz signs of regeneration and restoration o original structures, outweighing those fying injury and damage. "Balloon cells "acidophilic elements" are scarce, an infiltrates within the lobules are dimin in extent or have largely disappeared. those in the portal canals persist for time (Figs. 88, 89). Many of the K cells still contain lipofuscin, and the eration of parenchymal cells is clear parent from the varying sizes of the cells with prominent nuclei, and the multinucleated liver cells (Figs. 84 It is during this stage of predominant while clinical jaundice is on the wane disappeared entirely[216, 220] that stasis in the bile canaliculi often becomes ap in histologic preparations. This bile s regarded as a by-product of regenera liver tissue, repair of the gaps in t plates and the restoration of disrupt canaliculi. The newly formed live which are often much larger than th ture fellows (Fig. 84), may partia

TABLE 22. COMPARISON OF LABORATORY DATA ACCOMPANYING FIRST AND SECOND LIVER BIOPSIES IN 6 CASES OF ACUTE NONFATAL HEPATITIS

CASE NO.	AFIP ACC.	BIOPSY NUMBER	BIOPSY, DAYS AFTER		CEPHALIN FLOCCULATION	THYMOL TURBIDITY (UNITS)	SERUM CHOLINESTERASE (ΔpH/HR)	SERUM ALKALINE PHOSPHATASE*	URINE BILIRUBIN	SERUM BILIRUBIN MG./100 CC.		BILE THROMBI IN BIOPSY
			Symptoms	*Jaundice*						*One Minute*	*Total*	
9	319263	1	11	6	4+	8.1	0.5	11.5	3+	12	18.5	±
		2	21	16	3+	5.0	0.7	4.9	Neg.	3.1	5.9	+
11	319817	1	9	6	4+	8.1	0.4	11.4	2+	6.8	11.7	0
		2	20	17	Neg.	3.9	0.5	9.1	Neg.	1.0	2.0	+
14	320738	1	8	5	3+	9.8	0.7	14.1	1+	5.4	9.6	++
		2	20	17	Neg.	4.7	0.95	14.8	Neg.	0.9	1.8	±
15	322713	1	4	1	3+	5.4	0.68	7.1	1+	2.9	5.0	0
		2	24	21	3+	6.5	0.67	6.5	Neg.	2.7	5.8	+
16	323372	1	8	5	2+	2.9	0.88	6.4	Not det.	5.8	8.5	0
		2	33	30	Neg.	1.8	1.0	Not det.	Neg.	0.3	0.8	0
18	327042	1	6	4	4+	6.8	0.56	Not det.	Not det.	5.8	9.6	0
		2	26	24	Neg.	3.7	0.86	3.5	Neg.	1.0	2.0	+

* Modified Bodansky units. (Shinowara, G. Y., et al., J. Biol. Chem. **142**:921, 1942)

(From Keller, T. C., Giges, B., and Smetana, H. F.: Histopathologic study of acute nonfatal hepatitis, Mil. Surgeon **109**:425, 1951)

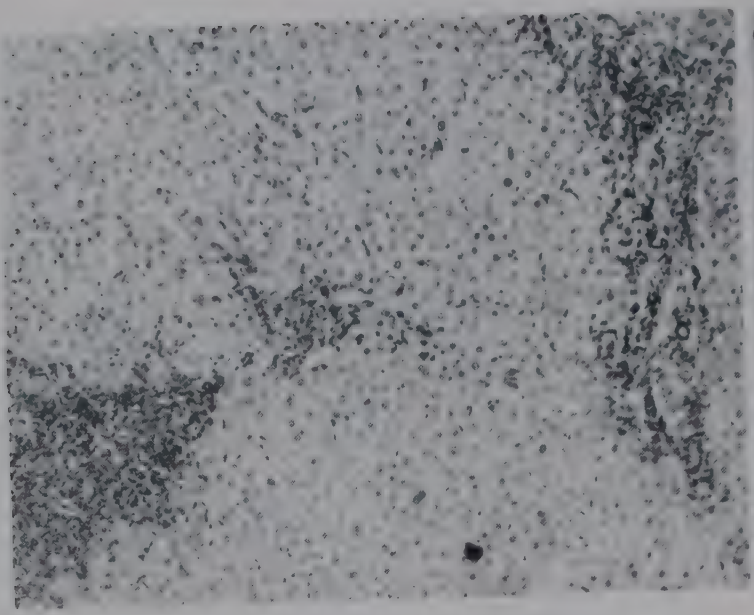


FIG. 90. Acute nonfatal infectious hepatitis. First needle biopsy of liver 53 days after onset of disease and 38 days after onset of jaundice. Prominent portal areas with monocytic infiltrates. Scattered focal necroses throughout the lobules, where the liver cells are moderately irregular. × 145. (Armed Forces Institute of Pathology, Acc. 485989-1)

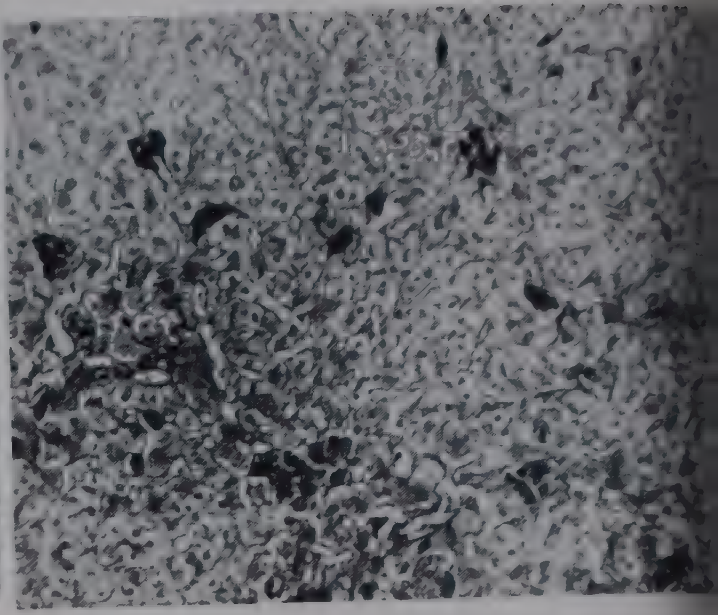


FIG. 92. Subsiding infectious hepatitis. Needle biopsy of liver 2½ months after onset of disease. Extensive iron deposits in and about Kupffer cells. Minimal histologic changes compatible with subsiding hepatitis. Gomori stain for iron. × 145. (Armed Forces Institute of Pathology, Acc. 286040)

temporarily obstruct the disrupted bile canaliculi, causing stasis of bile in blind passages until the walls are re-formed and the lumina regain their patency. However, interpretations differ at this point.[5, 18, 143,] The relationship between clinical jaundi in laboratory tests for serum bilirubin a the presence of bile thrombi in serial li biopsies is shown in Table 22. Within few weeks regeneration of liver cells a restoration of structural elements ha progressed to a point which permits the li to function normally. Gradually, the in trates in the portal canals fade away, a the histologic appearance of the liver comes indistinguishable from that of a n mal organ (Figs. 90, 91).

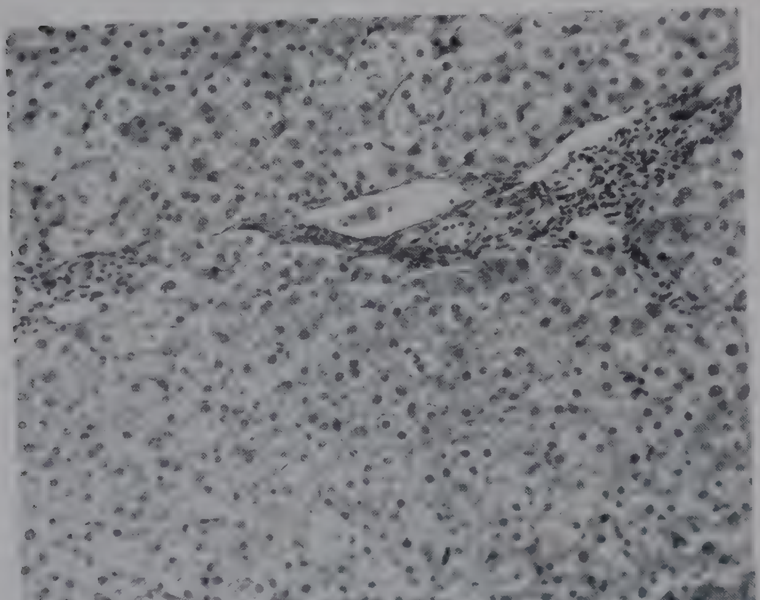


FIG. 91. Nonfatal infectious hepatitis, subsiding. Second needle biopsy of liver 9 months after onset of disease. Minimal residues of hepatitis characterized by slight enlargement of portal canals, containing a few wandering cells. Some irregularity of the liver cells; no retention of bile; no focal necroses. × 145. (Armed Forces Institute of Pathology, Acc. 485989-2)

However, it is conceivable that retur normal physiologic function to the liver c is not entirely synchronized with nor structure, since some time may elapse be the cells become adjusted to their mani activities. The tremendous regenera power of the liver has often been comme upon[15, 51, 181, 249] and probably follows d age to the liver parenchyma secondar disease, as well as loss of liver tissu surgical removal. In this connection important to remember that the retic fibers in infectious hepatitis are not si cantly disrupted or destroyed. Since th sions in acute nonfatal hepatitis are tered diffusely throughout the parenc

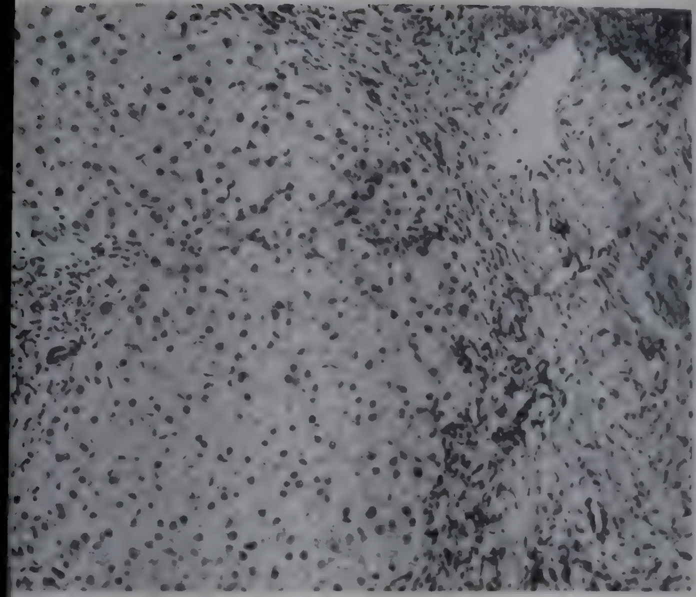


FIG. 93. Nonfatal infectious hepatitis,
ersistent. First needle biopsy of liver
months after onset of hepatitis. Promi-
ence of portal canals showing infiltrates
omposed of monocytes and increase in
ollagenous fibrous tissue. Occasional
ocal necroses throughout the lobules.
light irregularity of liver cells in some
elds. Lipofuscin is occasionally seen in
upffer cells. The architecture of the
ver is generally preserved, but enlarged
nd scarred portal triads cause some dis-
ortion. × 145. (Armed Forces Institute
f Pathology, Acc. 237741-1)

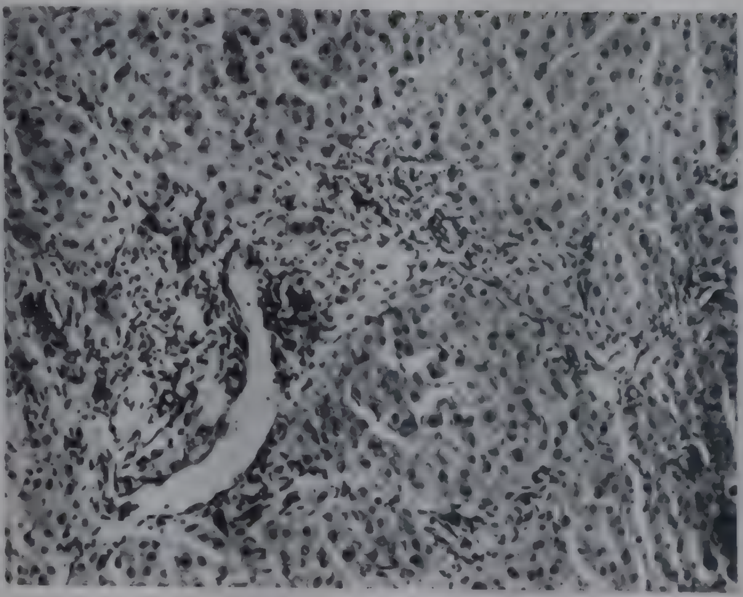


FIG. 94. Nonfatal infectious hepatitis, persistent. Second needle biopsy of liver 8 months after onset of disease. Moderate distortion of lobular architecture with occasional formation of pseudolobules. Scattered focal necroses throughout the parenchyma; lipofuscin in an occasional Kupffer cell. The portal canals are large, scarred and infiltrated with monocytes. × 145. (Armed Forces Institute of Pathology, Acc. 237741-2)

do not affect all liver cells, regeneration
proceed from preserved elements, along
lattice work of reticulum fibers, until the
nerating cell elements form liver-cell
mns, sinusoids and bile canaliculi. With
restoration of the lobules to normal form,
lipofuscin disappears from the Kupffer
s in a few weeks to several months after
sidence of the disease. After healing, in
omplicated cases of infectious hepatitis,
her scarring nor other signs of previous
age remain.

ertain minimal parenchymal changes,
n in liver biopsies from cases of subsiding
atitis, may be difficult to evaluate if no
vious biopsies were performed during the
id stage. Isolated focal necroses, occa-
al acidophilic bodies, residual portal in-
ates, lipofuscin in some Kupffer cells, and
tinucleated liver cells point toward sub-
ng hepatitis. In such cases a reliable clini-
history and results of clinical laboratory
s may suggest the possible cause of these
nges.

Special stains for iron performed on biopsy material from cases of subsiding hepatitis have sometimes demonstrated rather significant amounts of iron-containing pigment in Kupffer cells (Fig. 92). At first the pigment was regarded as evidence of hemosiderosis following blood transfusions, to which the hepatitis was also thought to be related. However, the same phenomenon was observed in patients who had not received transfusions. For this reason the iron pigment in Kupffer cells is now interpreted as a sign that the regenerated liver tissue has either not become adjusted to its role in iron metabolism or that an abnormal amount of ferritin is converted to hemosiderin pigment.

HISTOPATHOLOGY OF PERSISTENT NONFATAL VIRAL HEPATITIS

In occasional instances, infectious hepatitis does not recede but persists clinically. In such cases clinical symptoms often vary in intensity from time to time in the same patient, and the results of laboratory tests follow a similar pattern, suggesting periods

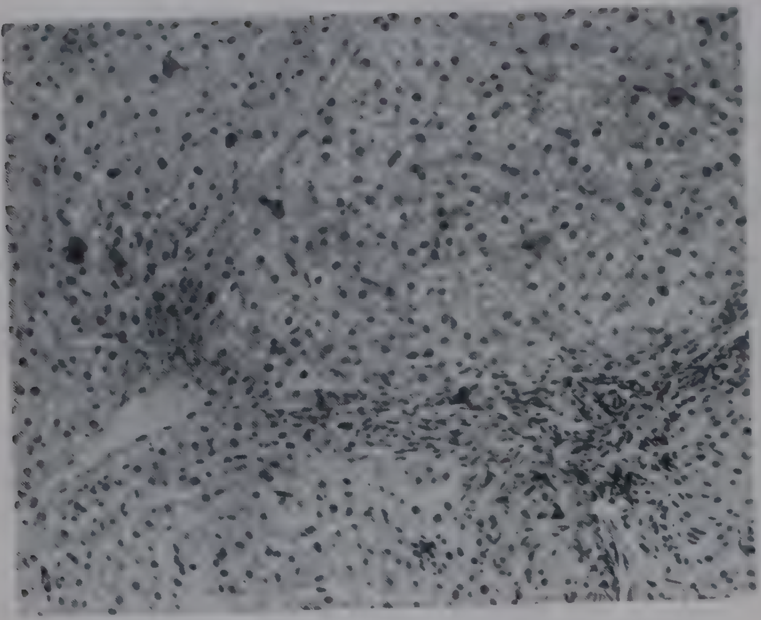


FIG. 95. Nonfatal infectious hepatitis, persistent. Third needle biopsy of liver 11 months after onset of hepatitis. Persistent moderate distortion of the lobular architecture and scarring of portal canals. Occasional focal necroses and moderate irregularity of liver cells. Some Kupffer cells contain lipofuscin. × 145. (Armed Forces Institute of Pathology, Acc. 237741-3)

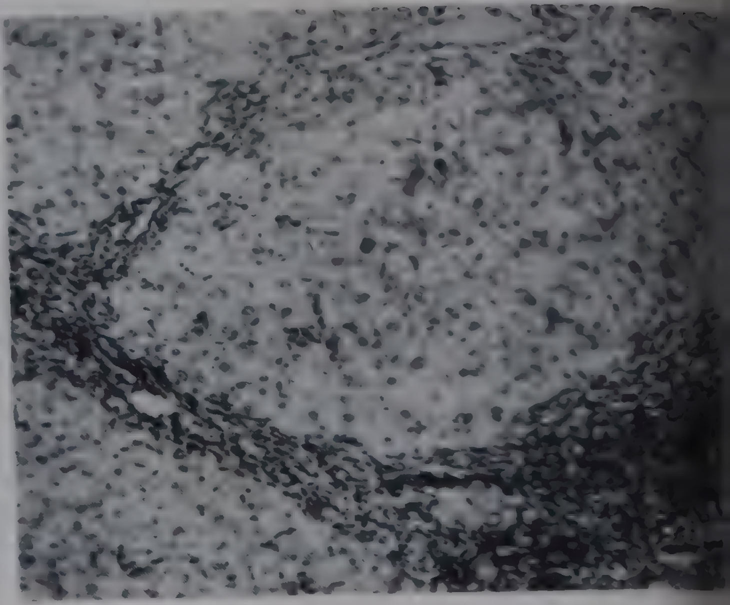


FIG. 96. Nonfatal infectious hepatitis, persistent. Fourth needle biopsy of liver 30 months after onset of hepatitis. Great distortion of lobular pattern, with formation of pseudolobules, occasionally carrying no centrally located efferent vein. Prominent monocytic infiltrates in portal areas; focal necroses in many parts of the parenchyma; lipofuscin in some Kupffer cells. × 145. (Armed Forces Institute of Pathology, Acc. 237741-4)

of temporary improvement followed by exacerbations. The degree of clinical jaundice also varies according to the amount of damage produced by the disease at the time. Such cases suggest a continuing process in the liver, with periods of apparent healing, followed by attacks of varying intensity, resembling those in the initial stage of the disease. Although in some instances this complication may be related to dietary indiscretion or perhaps to incidental damage of the liver by toxic substances, such as alcohol in excess, there are others in which no history of such incidental factors can be elicited. Therefore, we may assume that the agent causing hepatitis can persist in the liver, where it is capable of damaging liver parenchyma as in the original attack. Such persistent hepatitis is by no means unusual, even though it does not represent the ordinary course of events.

Clinically, such recurring attacks have been referred to as "delayed convalescence,"[146] "chronic infectious hepatitis" (chronic viral hepatitis,[212, 253] the posthepatitis syndrome,[127, 166, 212] posthepatic states[100]), designations which appear to be correct in so far as the time element is co cerned. The clinical diagnosis may be dif cult because of the vagueness of the con tion and the lack of specific tests f hepatitis.[127] Clinical jaundice is not a prom nent feature, although sometimes the seru bilirubin is increased. Bromsulfalein te may show retention, and cephalin floccu tion and thymol turbidity tests sometimes positive.

The histopathologic changes seen in opsy material from patients with "persist hepatitis" are fundamentally similar to th in acute infectious hepatitis except in deg and extent (Figs. 93 to 98). The alte tions are often so slight that they are ov looked or at least underestimated.[100, 115, 192, 207, 216, 220, 241] There is focal necrosis i cated by small groups of monocytes,[18 216, 218] presence of lipofuscin in s Kupffer cells, and monocytic infiltrate varying degree in portal canals. Acidop bodies are rarely seen, and retention of in bile canaliculi is not a feature. In s cases fibrosis of the portal canals ca recognized (Figs. 93 to 98). No si

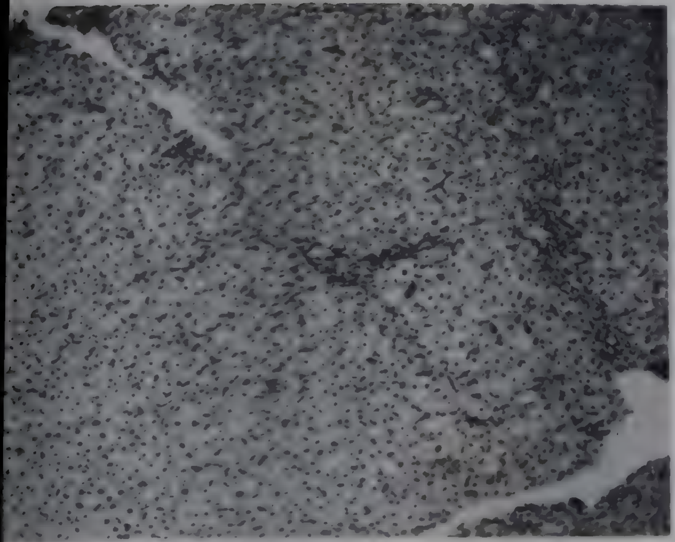


FIG. 97. Nonfatal infectious hepatitis,
rsistent. Fifth needle biopsy of liver
months after onset of hepatitis. Mod-
ate irregularities of the lobular archi-
ture and of liver cells. Some focal
croses. No pseudolobules encountered
this biopsy specimen. × 75. (Armed
rces Institute of Pathology, Acc.
7741-5a)

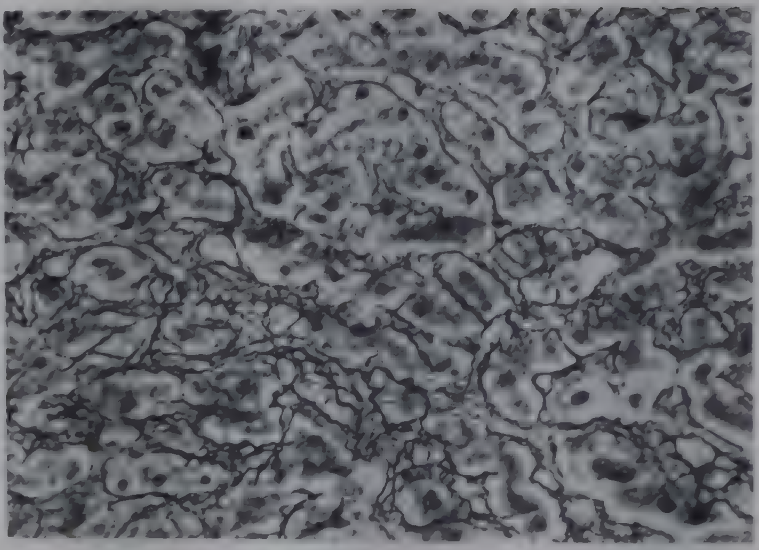


FIG. 98. Nonfatal infectious hepatitis, persistent. Fifth needle biopsy of liver 35 months after onset of hepatitis. Condensation of reticulum fibers, irregularly distributed through the lobules. Wilder reticulum stain. × 300. (Armed Forces Institute of Pathology, Acc. 237741-5b)

diffuse, permanent lesions or changes,
ly associated with "chronic inflamma-
' are produced in persistent hepatitis
te the chronicity of the condition. In
followed clinically, by repeated biop-
nd by laboratory studies, no disposition
rtal cirrhosis has been observed, even
several years of persistent clinical hepa-
Although in some instnaces, the fibrous
of portal canals was found to be in-
ed (Figs. 93 to 96), the relationship
een efferent veins and portal canals had
ined essentially undisturbed, and for-
on of pseudolobules was not generalized,
ugh it occurred occasionally and lo-
. Since portal cirrhosis is considered as
fuse process involving transformation of
entire parenchyma into pseudolobules
h lack centrally located efferent veins
are surrounded and separated from simi-
seudolobules by fibrous septa, such local
ing of isolated lobules does not consti-
portal cirrhosis.[34, 253]

is remarkable that in a majority of
, even after protracted "chronic hepati-
the liver tissue shows only minimal
ologic changes. It should be stated, how-
, that portal cirrhosis can occur in a
ent who has had epidemic hepatitis. The
factors that produce portal cirrhosis in a patient with no history of hepatitis may be equally active in the patient who has had the disease. It is not known whether an attack of hepatitis results in greater vulnerability of the liver to portal cirrhosis. As yet, evidence of the development of unequivocal portal cirrhosis following uncomplicated viral hepatitis has not been observed in the material available in the Registry of Hepatic Pathology.

Why is it that persistent hepatitis can last for such a long time? Since there is no evidence of a complicating coincidental infection, it is assumed, although not proved conclusively,[166] that the original virus infection persists. Apparently no immunity is produced in such instances, and it is possible that a state of tenuous equilibrium, reached between host tissue and virus, is upset when resistance is lowered temporarily. The role of possible damage of Kupffer cells in the prevention or retardation of formation of antibodies is not known. The condition of a precarious symbiosis between virus and liver cells resembles that observed in cases of chronic herpes infections of the mouth which may persist for years with temporary remissions and exacerbations.[117] Similarly, inclusion encephalitis, presumably a virus infection, can take a protracted course.[142]

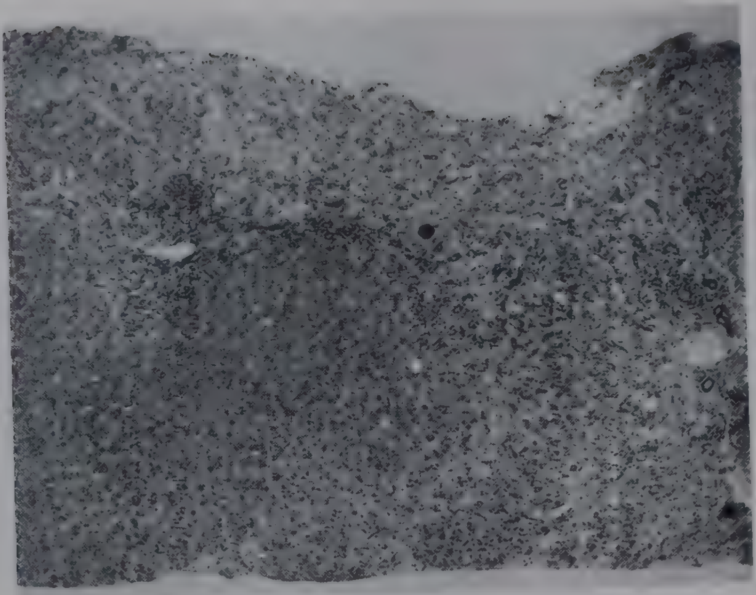


FIG. 99. Acute nonfatal infectious hepatitis. Needle biopsy of liver 1 month after onset of disease. Postnecrotic collapse. Distortion of lobular architecture, with widening of portal areas due to collapse of reticular stroma, and early scarring. Monocytic infiltrates in portal areas; many small bile ducts. Small nodules of regenerated liver cells are seen in the scar tissue. × 65. (Armed Forces Institute of Pathology, Acc. 506130-a)

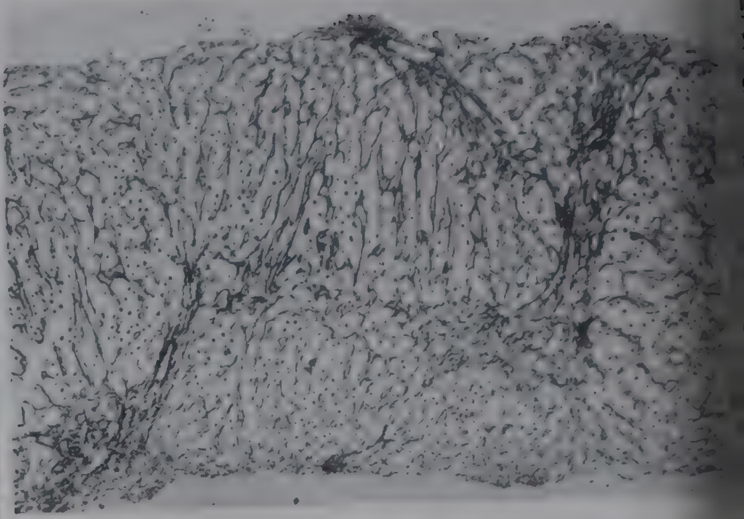


FIG. 100. Acute nonfatal infectious hepatitis. Postnecrotic collapse. Needle biopsy of liver 1 month after onset of disease. Irregular condensation of collapsed reticulum and distortion of lobular architecture. Wilder reticulum stain. × 65. (Armed Forces Institute of Pathology, Acc. 506130-b)

POSTNECROTIC COLLAPSE AND POSTNECROTIC SCARRING

In some instances of clinical infectious hepatitis, biopsy sections show areas of necrosis of comparatively large, confluent groups of liver cells, irregularly scattered through the lobules (Figs. 99, 100). Some of these lesions may occupy a considerable portion of individual lobules and even extend to neighboring lobules. In general, there is no constant relationship of these areas of necrosis to any preformed hepatic structures, such as efferent veins or portal canals. On the contrary, it often appears as if portions of liver tissue were gouged out of the parenchyma. Within these areas of necrosis, of the former parenchyma only the reticulum fibers, the walls of the capillaries with their endothelial lining cells, and Kupffer cells remain (Fig. 100). Due to lack of supporting liver cells the stroma collapses and forms condensations of fibers, imitating fibrous connective tissue which appears to traverse the parenchyma. Monocytes and other inflammatory cells are scattered through the collapsed stromal elements, and other typica histopathologic signs of hepatitis, such a acidophilic bodies, balloon cells, and lipo fuscin in Kupffer cells are observed. Th limited amount of liver tissue and the disrup tion of the normal architecture seen in th needle biopsy material sometimes makes th diagnosis difficult and may be responsible f the mistaken one of portal cirrhosis. How ever, even in the early stages, alteration liver lobules is much too irregular for port cirrhosis; most of the efferent veins are place, particularly if the center of the lobu is not involved in the process, and the ap parent scar tissue is actually composed closely packed reticulum fibers.

Postnecrotic collapse, then, is the morph logic expression of a single severe injury the liver parenchyma by the virus of infe tious hepatitis, leading to sudden simultan ous necrosis of groups of liver cells. Aft the debris of the necrotic cells is remove the stroma is left behind. Liver cells a regenerated and, in absence of complic tions or renewed attacks, healing can ta place. The reason for this deviation fr the more common diffuse involvement the liver tissue by the virus is not know nor can it be related with certainty to a m severe form of clinical disease. Perhaps group of variables, such as the state ance, the virulence of the virus, the f the patient, or local hepatic conditions unt for this variant of viral hepatitis.

e diagnosis of postnecrotic scarring is ied when the architecture of the liver is picuously disturbed and the reticulum s are replaced by collagenous fibers. This ition probably takes place when regen- on of the destroyed liver cells proceeds e slowly than replacement of reticulum s by collagenous connective tissue fibers. results in an irregular partition of the tissue, without regard to the natural itecture, by fibrous scars which occupy place of the collapsed stroma.[248] The lar pattern is altered thereby, unpredicta- but characteristically. The final fate of e scars is not known, but it has stated that eventually they may ppear.[18, 34]

dvanced postnecrotic collapse may merge erceptibly with postnecrotic cirrhosis, se lobular cirrhosis or nodular hyper- ia following acute viral hepatitis.[248]

nce the damage by postnecrotic collapse es neither uniform nor generalized in- ement of the tissue, symptoms of hepatic fficiency and signs of portal hypertension its consequences are not encountered, ss significantly large portions of the par- nyma have been destroyed and replaced car tissue. The absence of pseudolobules generalized perilobular scarring and s of persistent infectious hepatitis, if ent, will contribute to the correct histo- ologic diagnosis even in needle biopsies. clinical history will also be of consider- help in differentiating between portal nosis and postnecrotic scarring. A possi- relationship between viral hepatitis and al cirrhosis has been suspected[1, 5, 7, 34, 248] but cannot be proved without a thor- h statistical analysis to indicate whether atitis is more often a background of portal hosis than can be attributed to chance ne. After all, nutritional as well as toxic nage of the liver may occur in persons have had viral hepatitis.

COARSE NODULAR CIRRHOSIS

(Postnecrotic Cirrhosis, Posthepatitic
Nodular Hyperplasia, etc.)

here is circumstantial evidence that coarse nodular cirrhosis may be one of the late but infrequent consequences of infectious hepatitis.

Clinically, coarse nodular cirrhosis is difficult to differentiate from portal cirrhosis without the history of an episode of viral hepatitis; moreover, similar consequences are reported after toxic damage of the liver by phosphorus and arsenic, or mushroom poisoning.[91, 127] All these agents are capable of producing necrosis of liver cells followed by regeneration, scarring and distortion of the hepatic architecture. The symptoms produced by the late effects of these agents can be explained by the development of portal hypertension or hepatic insufficiency, or both. Portal hypertension leads to ascites, splenomegaly, caput medusae, varices of the veins of the esophagus and of other overtaxed collateral venous portacaval anastomoses, with possible rupture and hemorrhage into the gastro-intestinal tract. Hepatic insufficiency, indicating a deficit in required liver tissue resulting from inadequate regeneration, usually is followed by coma and death.

The gross and histopathologic picture as seen in the final stages of this condition is unmistakable and is characterized by the replacement of the usual liver parenchyma by nodules which measure 1 cm. or more in diameter and project above the capsular surface; they are clearly separated by septa made up of bands of fibrous tissue which are often thick and dense. The organ is much smaller than normal and is sometimes misshapen. The liver tissue is dense to hard in consistency and it may be jaundiced. The capsule is frequently thickened, with adhesions to surrounding structures. On cross section the nodules are tan, brown, or bile-stained, and individual nodules may vary greatly in appearance; the septa are grayish white or grayish red in color.

Microscopically, the nodules are composed of groups of individual liver lobules showing liver cell columns radiating from efferent veins toward portal triads. The liver cell columns are fairly regular, even if not always showing perfect radial alignment, and they are flanked by sinusoids; the reticulum fibers and the Kupffer cells appear to be unchanged. Most of the portal triads are much smaller than normal, as are their vessels and biliary channels; often portal canals and efferent veins are irregularly spaced. These composite nodules are partly or completely surrounded by bands of fibrous connective tissue, varying in thickness and containing bile ducts and vessels. Depending on the age of the process, there may be residues of inflammation characterized by infiltrates, active regeneration of liver cells and increase in the number of small bile ducts.

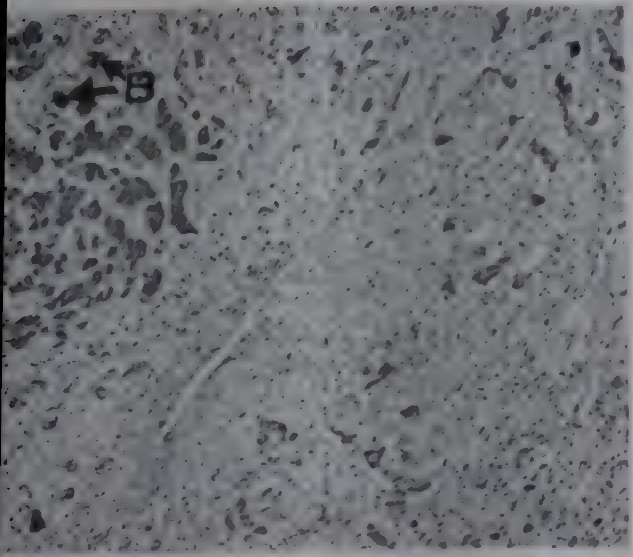
Although the appearance of the liver in portal cirrhosis is obviously similar to that in coarse lobular cirrhosis except for the size of the nodules, the histopathologic details suggest a fundamentally different pathologic background for the two conditions. In portal cirrhosis individual liver cells or small groups of these elements are destroyed, along with the local reticulum fibers, and this process is followed by atypical regeneration of liver cells. This leads to collapse of the stroma and eventual fibrosis, with formation of irregular, often concentrically arranged, regenerated groups of liver cells which lack proper radial orientation. In brief, portal cirrhosis represents the result of damage to each individual liver lobule, leading to the formation of a pseudolobule, lacking a centrally located vein. The tissue comprising the nodule in coarse lobular cirrhosis, on the other hand, is made up of several groups of individual liver lobules having a fundamentally normal, if somewhat distorted, architecture. Regeneration of the liver tissue following infectious hepatitis proceeds in a more orderly fashion, presumably due to the preservation of the reticulum fibers. Despite their different histologic appearances, the consequences of the two may be clinically indistinguishable.

In some cases the development of coarse nodular cirrhosis can be traced to clinical hepatitis in the past. The time elapsed between the attack of hepatitis and the development of cirrhosis varies considerably. It may be years[127] before the final stage is reached, but the history of an attack of hepatitis several months previously seems to be more common.

Neither the histogenesis nor the pathogenesis of coarse nodular cirrhosis is actually known. The explanation concerning its formal pathogenesis, as developed by Thaler,[230] is interesting but difficult to f
low. The Registry of Hepatic Pathology h
not yet accumulated series of biopsies depic
ing the stages in the development of th
condition, and therefore its evolution is co
jectural, a matter of collective experienc
pieced together from bits of evidence an
from comparisons with cases of hepati
having some features in common with the
of coarse nodular cirrhosis. It seems plausib
to assume that a severe, initial, subfa
injury by the virus of infectious hepatitis c
cause sudden destruction of large conflue
portions of liver tissue throughout the orga
with rather even distribution of the lesio
throughout the lobules. Although the dama
may be extremely severe, liver cells whi
have escaped destruction can engage in
generation of liver parenchyma. Regene
tion apparently has to proceed undisturb
in order to succeed in replacing the destroy
parenchyma with masses of liver cells wh
are gradually organized into groups of fai
regular lobules. Branches of surviving sm
bile ducts can be seen extending from
septa between nodules into the regenera
liver lobules to form portal canals, usua
much smaller than those in a normal li
In the same fashion efferent veins are
stored, so that the final lobular architect
within the nodules is reasonably similar
that seen in normal liver. After the group
regenerated lobules have filled out the sp
created by the parenchymal necrosis, t
expansion is limited by the growth of
jacent lobules from which they are separ
by septa made up of the former retic
stroma, the former portal triads and wal
sinusoids of destroyed liver tissue.

There can be no serious interferenc
the development of these groups of lob
particularly not by recurring hepatitis
cause this produces entirely different h
pathologic consequences. In areas of
plete destruction of liver cells, no rege
tion can take place, and only the p
triads, Glisson's capsule, the stroma
capillaries and Kupffer cells remain.

The separation between parts of live
sue which are normally coherent, as w
abnormal portacaval anastomoses, see
create difficulties in circulation, so that
hypertension eventually ensues, and th



G. 101. Subacute fatal infectious
titis; death 68 days after onset of
s. Small island of regenerated liver
showing an irregular arrangement of
columns. Stasis of bile in small bile
at the periphery of the lobule at
Most of the section shows collapsed
na containing surviving and appar-
proliferating small bile ducts but no
nerating liver cells. × 55. (Armed
es Institute of Pathology, Acc.
26)

ces are those usually associated with
d collateral circulation. Necrosis of
f the nodules may occur, probably on
xic basis, either due to anemia follow-
horrhage or in relation to local circula-
fficulties; in such instances, hepatic
iency usually results.

lar necrosis, reminiscent of infarction,
rved sometimes in the pseudolobules
al cirrhosis. It is significant that this
cation also commonly occurs after
hemorrhage from rupture of a varicose
Despite the suggestive relationship to
nia, sometimes this complication is
eted as the effect of viral hepatitis on
r in portal cirrhosis.

FATAL VIRAL HEPATITIS

ute Yellow Atrophy, Subacute Red
phy, Catarrhal Jaundice, Epidemic
ndice, Fulminant Hepatitis, etc.)

**cepts Concerning the Pathology and
pes of Fatal Viral Hepatitis.** The most
e form of viral hepatitis is that in
the severity of injury to the liver is
patible with life. Rokitansky,[196] in

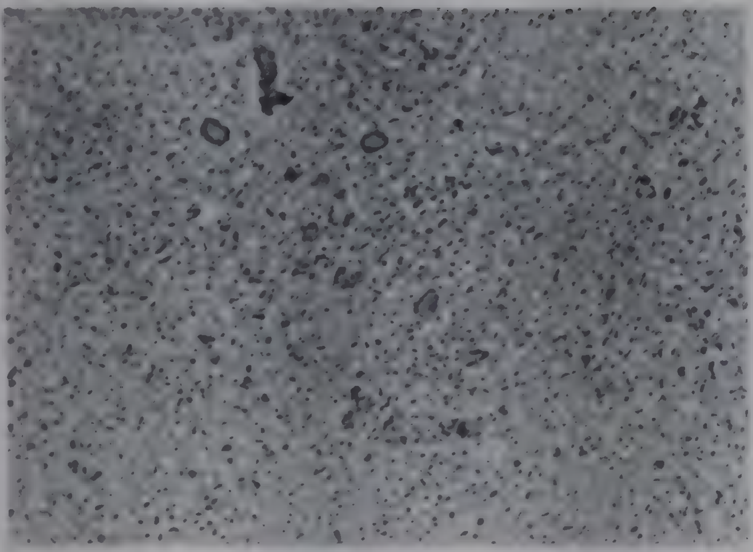


FIG. 102. Acute fatal infectious hepatitis. Death 20 days after onset of infectious hepatitis, 14 days after onset of jaundice. Total necrosis of liver cells of all lobules with preservation and proliferation of interlobular bile ducts. × 125. (Armed Forces Institute of Pathology, Acc. 548232)

1842, recognized the changes in the liver as the important factor in this most severe form of jaundice and introduced the expression "acute yellow atrophy." In 1845, Busk[19] described the disruption and the disintegration of liver cells as observed microscopically. Zenker[255, 256] and Klebs[119] furnished additional details of these microscopic changes, while Waldeyer,[242] in 1868, recognized the significance of regeneration of liver cells in the interpretation of the gross and the microscopic appearances of the diseased tissue. Since then numerous authors[91, 144, 145, 154, 194, 201, 202, 203, 257] have contributed to the understanding of the relationship between the clinical picture, the physiologic adaptation and the histopathologic alterations encountered in "acute yellow atrophy," but only recently has it been accepted as the extreme form of epidemic hepatitis. A possible relationship had been suggested on clinical grounds by various observers,[8, 14, 22, 42, 52, 128, 190, 239, 244] but it was not until the use of needle biopsy of the liver, which made it possible to follow the progression of the pathologic changes, that the ideas and the observations of Eppinger[43] were generally accepted. The comprehensive studies of the pathology of the several forms of fatal hepatitis by Lucké[131] and Lucké and Mallory,[133]

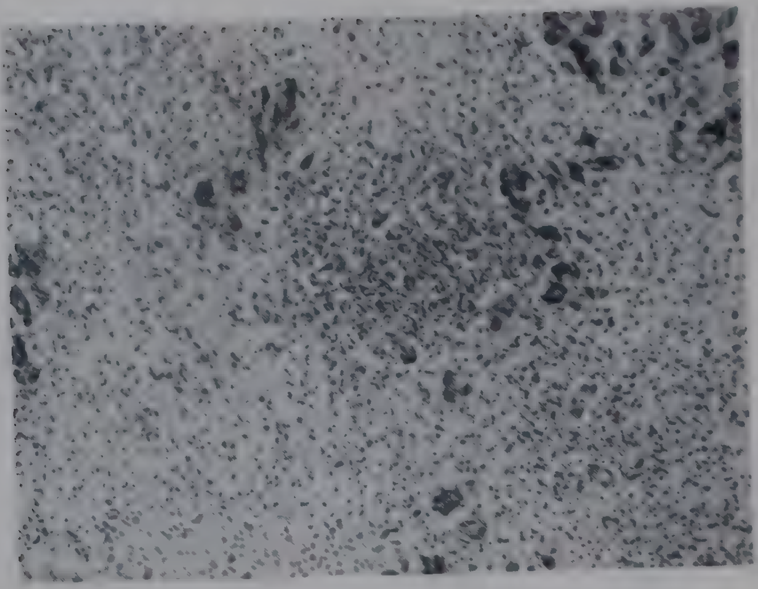


FIG. 103. Acute fatal infectious hepatitis. Death 20 days after onset of hepatitis, 14 days after onset of jaundice. Total necrosis of liver cells of all lobules with preservation and proliferation of interlobular bile ducts. Massive monocytic infiltrates situated in portal areas. × 125. (Armed Forces Institute of Pathology, Acc. 548232)

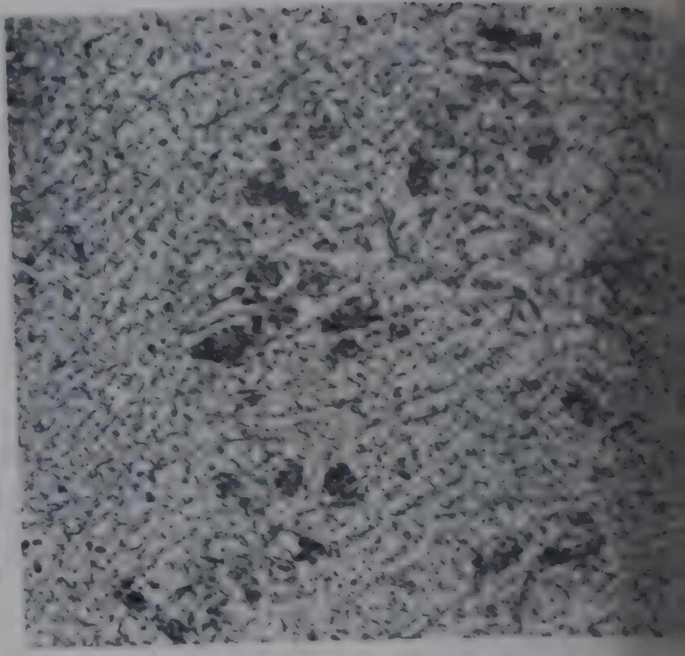


FIG. 104. Acute fatal infectious hep
titis. Death 20 days after onset of hepa
tis, 14 days after onset of jaundic
Surviving islands of liver cells and b
ducts embedded in collapsed and co
densed reticulum fibers. Wilder reticulu
stain. × 125. (Armed Forces Institute
Pathology, Acc. 548232)

have contributed materially to the understanding of the disease.

Gross Pathologic Findings in Fatal Viral Hepatitis. The liver is usually smaller than normal, weighing in the neighborhood of 1,200 Gm. and sometimes much less. The surface of the organ is smooth, but its capsule may be wrinkled. The liver tissue is very flabby. On cross section the parenchyma is often of a peculiar ochre-yellow color in the early phases (acute yellow atrophy), later turning dark red (subacute red atrophy) (Plate 1).

The peculiar gross appearance of the liver in this disease is the result of coloring of the residual stromal tissues by bile, following necrosis of the liver cells. The decrease in size of the organ can be ascribed to the disappearance of most of the necrotic parenchymal cells, leaving practically nothing but the reticulum, the sinusoids and the portal canals of Glisson's capsule. The change in color from yellow to red in the later phases is the result of passive filling of the sinusoids with blood when the supporting pressure of liver cells on the capillaries is no longer exerted.

The length of survival after a severe attack of hepatitis is dependent on the amount of functioning liver tissue; therefore, the lo
the interval between onset of disease
death, the more regenerated liver tissue
be in evidence. The architecture of the
formed liver parenchyma usually differs
the normal: instead of columns of liver
radiating from efferent veins there is
hazard and even concentric arrangeme
the cells composing the regenerated is
with no constant relationship to central
and portal canals (Fig. 101); in time
tissue in such areas shows jaundice, ne
and congestion, contrasting with th
lapsed and inert portion of the organ
regeneration of parenchymal cells is
ently impossible.

In about 15 per cent of instances
hepatitis, parts of the gastro-intestina
may be edematous and show phleg
inflammatory changes, most promi
the submucosa. Ascites, too, is co
Jaundice is practically always in e
with rare exceptions, such as in insta
fulminant hepatitis where there has n
time for the diffusion of bile pig
where the damaged reticuloendothe
tem is perhaps incapable of forming b

Histopathology of Fatal Viral H

pically, the gross changes of the
'acute yellow atrophy" are reflected
llular alterations of the parenchyma.
ulminant type of hepatitis the liver
ve largely disappeared (Figs. 102,
ne of the most remarkable features is
ral preservation of the architecture of
nchyma: the efferent veins are lo-
the center of the lobule, and the
s radiate from there toward the
y. The reticulum is in a remarkably
te of preservation (Fig. 104), as are
ffer cells and other stromal elements.
tal triads contain the usual structures
w infiltrates composed of inflamma-
ls, particularly monocytes, lympho-
d plasma cells (Fig. 103), in addition
rying number of eosinophils and
phonuclear leukocytes. In essence,
stromal skeleton of the liver lobule
4) is preserved and this is, of course,
tible with life. Remnants of liver tis-
ch have escaped destruction are usu-
nd in the periphery of the lobules.
rwhelming predominance of necrotic
in the center of the lobules is largely
postmortem autolysis and usually is
n in biopsies.[18]

microscopic changes in other organs
increase in cellular elements in the
and congestion of the sinusoids,
and lymphoid hyperplasia of lymph
ome hyperplasia of the bone marrow,
c nephrosis and phlegmonous inflam-
of the gastro-intestinal tract, predomi-
n the cecum. Degeneration of ganglion
d a mild form of meningo-encephali-
e brain stem, the hypothalamus and
basal ganglia are seen in cases in
coma has been secondary to fatal
ic hepatitis. These changes resemble
en in the brains of experimental ani-
ying in hepatic coma. Hemorrhages
ally present in the endocardium and
ardium, in the lungs, the kidneys and
stines; these are probably attributable
rbances of the vitamin K metabolism
the lowering of the level of prothrom-
condary to the liver lesion.

rpretation of Gross and Microscopic
s in Fatal Viral Hepatitis. The in-
ation of the two outstanding com-
s dominating the gross picture in acute
fatal viral hepatitis has undergone many changes and has been the subject of many controversies.[7, 19, 91, 119, 120, 144, 145, 154, 194, 196, 242, 255, 256, 257] It is now generally accepted that the peculiar orange and ochre-yellow appearance of the liver tissue is characteristic of the acute phase of hepatitis during which the liver parenchyma shows signs of severe degeneration and necrosis, while the "red substance" represents the end stage of the process resulting from complete destruction of the liver parenchyma, leaving only bile ducts, stroma and passively dilated sinusoids. The gross appearance of the liver during the red stage has often been compared with that of the spleen; it is also similar to that of the atelectatic lung in which the alveoli are collapsed and blood vessels become prominent due to passive congestion. The red areas consist practically of supporting tissue only, and therefore their consistency is much denser than that of the yellow areas.

"Acute yellow atrophy" may be limited to a portion or portions of the liver; it may affect a whole lobe or the entire organ. The area of atrophy is possibly related to the extent of the damage produced in certain parts of the organ, which, in turn, is said to depend on the distribution of portal blood flow within the liver.[94] The gross appearance of the liver between the stage of acute liver necrosis and red atrophy is characterized by the blending of various shades of yellow, orange, greenish yellow, ochre, brown, red to bluish red, depending on the various tissue elements present or absent. Regenerated liver tissue appears sharply and distinctly defined from the red background by its yellowish brown tint and it usually protrudes from the freshly cut surface of the liver as though it had been under pressure (Plate 1). It is in sharp contrast with the irregularly outlined, flat, soft yellow areas during the early stages of "acute yellow atrophy," which connote degeneration and necrosis of liver tissue. The complicated gross picture seen during the late stages of subacute red atrophy is the result of necrosis of regenerated liver tissue, persistence and apparent proliferation of intralobular bile ducts, renewed regeneration of liver cells, collapse of stroma, icteric coloring of tissues, and retention of bile in some bile capillaries, presence of inflammatory infil-

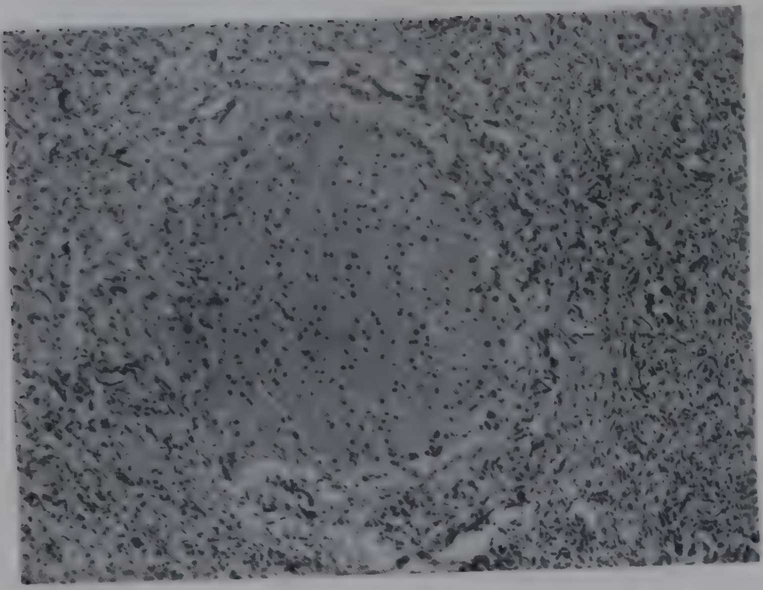


FIG. 105. Acute fatal infectious hepatitis; death 2 weeks after onset of illness. Regenerated pseudolobule embedded in collapsed stroma containing small bile ducts. Poor orientation of regenerated liver cells. No evidence of efferent vein. × 115. (Armed Forces Institute of Pathology, Acc. 170637)

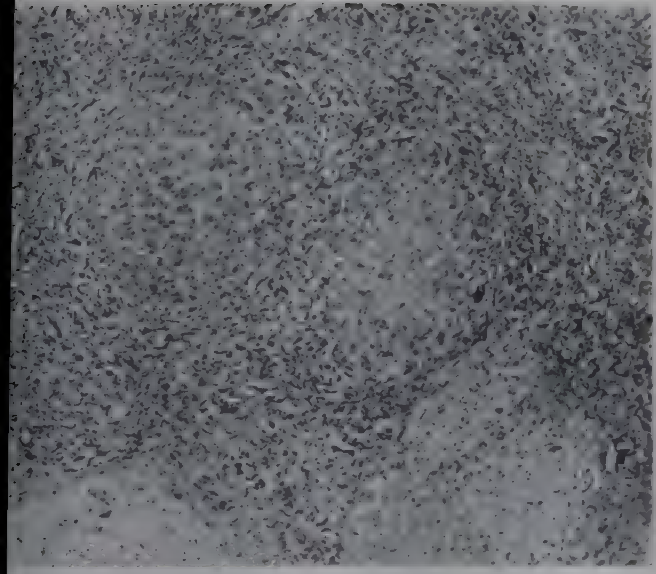
trates, lipofuscin in Kupffer cells and passive dilatation of sinusoids.

After injury has occurred, regeneration is initiated almost immediately by cells that have escaped damage, either in many parts of the parenchyma or in limited areas. Grossly, this regeneration of liver cells is recognized by the presence of well-outlined nodules of yellowish brown tissue situated in the grayish-red portions of necrotic, collapsed liver parenchyma (Plate 1). The regenerated nodules of liver parenchyma are composed of adenomalike groups of liver cells whose architecture does not conform exactly to that of regular liver lobules; there is no centrally situated vein from which liver cell columns radiate toward the periphery (Figs. 101, 105). Septa composed of collapsed reticulum and collagenous fibrous tissue of pre-existent stroma elements surround the nodules, thereby separating them from similar regenerated lobules. In these capsule-like septa there are many small bile ducts (Figs. 101-105). The apparent increase in their number is in part, at least, attributable to collapse of necrotic liver tissue with survival of some of the more resistant bile passages; however, active proliferation has also been reported in the neighborhood of regenerated liver tissue. Although regeneration
liver cells from bile epithelium has of
been asserted,[181] it never has been pro
conclusively or denied categorically. The
parent transformation of the epithelium
proliferating intralobular bile ducts wh
were spared during the attack of hepat
has also been interpreted as an attempt
these structures to link up with regenera
liver cells.[140] In areas of "red atrophy" w
completely destroyed liver parenchyma, s
viving biliary channels may be seen, wh
show no evidence of attempts at transfor
tion into liver cells (Figs. 101, 105). In ca
of protracted fatal hepatitis the regenera
liver tissue often undergoes degeneration
necrosis which nullify the attempted for
tion of new parenchyma (Figs. 106, 107)

The extreme form of this sudden c
strophic and specific destruction of pra
cally all parenchymatous elements of
organs of the body is indeed remarkable
amounts to almost complete removal of
liver, with elimination of its metabolic
catabolic functions. The reason for this
minant variant of hepatitis is unknown.
haps the infectious agent is present in
overwhelming quantity as to smother
defenses, or resistance of the liver is so
as to permit complete destruction of
organ.

The rapid clinical course and striking
croscopic features in the fulminant for
hepatitis suggest a simultaneous attac
practically all liver cells, not only k
them instantly but also causing their
tegration. There is no gradual "fading a
of damaged liver cells, leaving ghos
cells, or coagulation necrosis transfor
organized cells into masses of amor
debris. Whatever is left of the dead ele
is either carried away into the circulati
dissolved and absorbed.

No regeneration of liver cells is obs
in cases of fulminant hepatitis because
cells, capable of division, are com
lacking. Inflammatory reaction is mi
partly because the time was too sh
permit its development, and perhaps b
Kupffer cells were damaged. The infl
tory infiltrates observed in and abo
lumen of central veins are thought to
sent wandering cells, laden with deb



IG. 106. Acute fatal infectious hepa-
with death 2 weeks after onset of
ss. Several regenerated pseudolobules
edded in collapsed stroma of de-
yed liver tissue and containing many
ll bile ducts. Varying degrees of
osis of regenerated pseudolobules.
75. (Armed Forces Institute of Pa-
ogy, Acc. 170637)

ing into the efferent vessels. Some of
cells contain lipofuscin, derived from
c liver cells.[131] In the more protracted
f fatal hepatitis enough liver cells must
alive to keep up the basic function
organ. If comparison with the data
l from experiments on animals is per-
e, at least one fourth of the liver tissue
ired to sustain life.[51]

question of complete restitution of
er and its function after a severe at-
f "acute yellow atrophy" has been
often but never has been answered
itatively. Perhaps the best possible
of healing following a near fatal injury
nfectious hepatitis is the development
rse lobular cirrhosis in which the re-
tion of liver tissue exceeds the basic
ement of parenchyma necessary to sus-
e.

at causes the differences between fatal
onfatal hepatitis? Lack of information
ning the nature of the infectious agent
s relationship to liver cells, as well as
to find a susceptible laboratory ani-
ake this a difficult question to answer.
there is much variation in severity,
on, clinical and pathologic manifesta-
even between individual cases of fatal viral hepatitis, it might be suggested that milder manifestations of the disease are due to an attenuation of the infectious agent. The occasional occurrence of fatal cases in epidemics of predominantly nonfatal hepatitis is well known and supports the assumption of a common infectious agent.

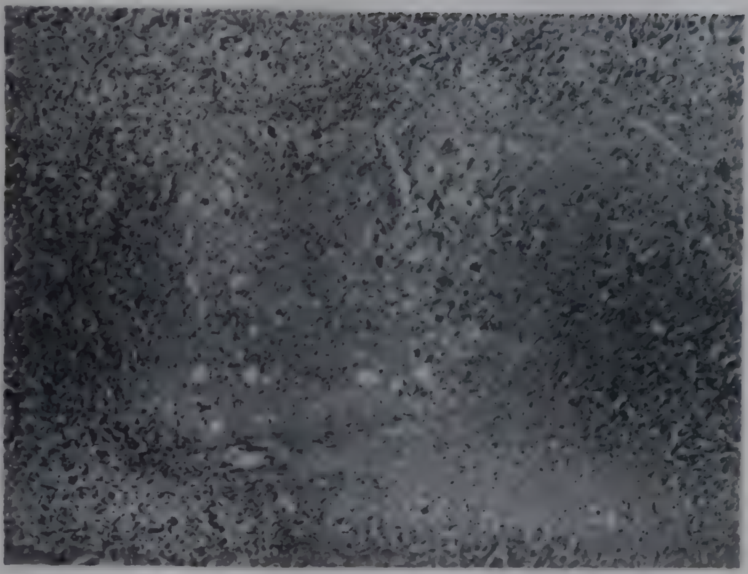


FIG. 107. Acute fatal infectious hepatitis, with death 2 weeks after onset of illness. Complete necrosis of regenerated pseudolobule, embedded in collapsed stroma of former liver parenchyma. × 75. (Armed Forces Institute of Pathology, Acc. 170637)

In the nonfatal type, liver cells are affected individually, and as the disease spreads through the lobules, the destruction it leaves behind is followed almost immediately by regeneration. It seems possible that immunity develops in the majority of nonfatal cases, so that restitution of the parenchyma can proceed without further interference.

In the persistent type of hepatitis the attacks occur at irregular intervals and are followed by regeneration. The lesions are of varying intensity and are usually focal in nature. Virulence of the infectious agent, immunity and resistance phenomena must all be invoked to explain this rather atypical facet of hepatitis.

Sharp attacks of hepatitis of limited duration and extent, but affecting coherent groups of liver cells, cause the simultaneous destruction of adjoining portions of lobules with consequent collapse of the supporting reticular stroma. This condensation of the reticulum with its irregular distribution and

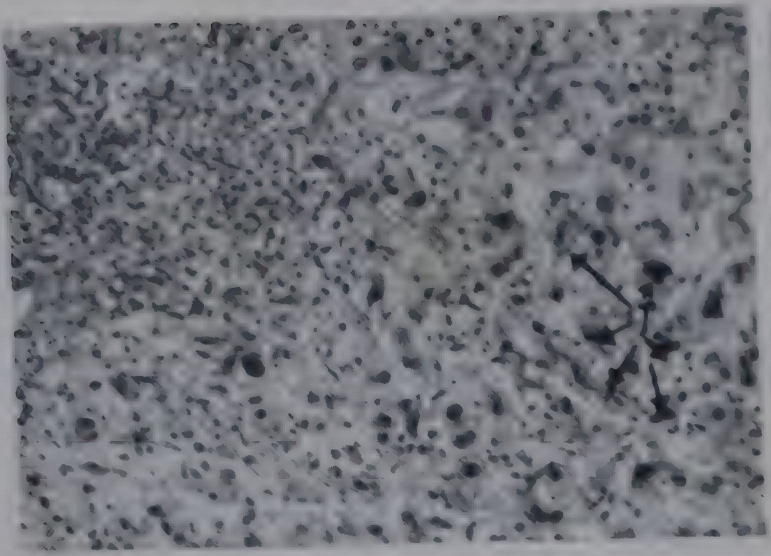


FIG. 108. Acute nonfatal infectious hepatitis, with pericholangitis. Needle biopsy of liver 12 days after onset of hepatitis, 9 days after onset of jaundice. Portal infiltrates consisting mainly of polymorphonuclear leukocytes. Irregularity of liver cells with formation of numerous acidophilic bodies and binucleated forms. Bile retention in canaliculi, particularly in center of lobules at "T." Focal monocytic infiltrates in sinusoids throughout lobules. × 195. (Armed Forces Institute of Pathology, Acc. 567009)

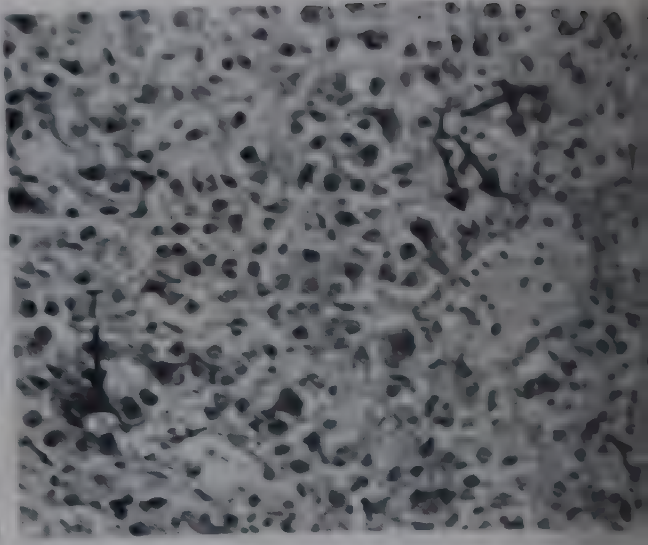


FIG. 109. Acute nonfatal homolog serum hepatitis with pericholang Needle biopsy of liver 1 month a onset of hepatitis. Marked irregularit liver cells which often show degenera changes and formation of acidop bodies. Obvious stasis of bile in can uli, particularly about efferent veins "T." × 300. (Armed Forces Institut Pathology, Acc. 528275)

resulting distortion of the pre-existent preserved hepatic tissue is often mistaken for an active cirrhotic process, when it actually represents only an apparent increase in stromal elements. However, if regeneration is retarded, scar tissue formation may be seen in areas of collapse of the reticular stroma; perhaps this permanent distortion is best referred to as "postnecrotic scarring."

The devastation of the liver tissue in cases of fulminant viral hepatitis is only an exaggeration and generalization of the lesions seen in nonfatal hepatitis. It is probably this type of near fatal injury which causes almost complete destruction of the liver and leads to adenomalike hyperplasia of regenerated liver cells, eventuating in coarse lobular cirrhosis.

ATYPICAL FORMS OF VIRAL HEPATITIS

Anicteric Viral Hepatitis. A number of writers, particularly those interested in the clinical and the epidemiologic aspects of epidemic hepatitis,[11, 14, 22, 24, 30, 34, 73, 82, 90, 100, 123, 127, 143, 161, 163, 170] have referred anicteric form of viral hepatitis whi sents the clinical features usual for h such as fatigue, anorexia, abdomina headache and nausea, distaste for s tenderness over the liver and hep largement. The thymol turbidity test to be the most reliable of the laborat cedures in this disease, but cephalin tion tests are also positive in n stances.[30] The serum bilirubin level cases is below 2.0 mg. per cent. The d rests mainly on clinical symptoms o tis and on a certain tendency to ch development of cirrhosis in the wak condition has been suspected,[122, 1] though its origin from a nonicteric hepatitis is rather difficult to estab absence of jaundice has baffled clini pathologists, and as yet a good ex for this phenomenon has not been It has been suspected that prompt patients with acute infectious hep less likely to develop jaundice than patients. According to Mallory,[148] teric form can be distinguished cally from its icteric counterpar presence of bile thrombi in condition.

athologically, infectious hepatitis
liagnosed only if characteristic le-
found in the liver. Since histologic
of icterus is rarely apparent in the
nase of the nonfatal variety, the
of bile thrombi in bile capillaries is
dered as diagnostic, as they are usu-
arent only in a later phase when
aundice is on the wane or has dis-
. No unequivocal instance of acute
anicteric hepatitis is recorded in the
e Armed Forces Institute of Pathol-
ases of persistent infectious hepati-
ds of absence of clinical jaundice
nal levels of bilirubin are not un-
, while residues of histologic lesions
sist.

ericholangitic Form of Viral Hepa-
ome cases of clinical viral hepatitis
biopsy shows a histopathologic pic-
is somewhat different from the ordi-
addition to the alterations usually
epatitis (Fig. 108) there is definite
tion, even in the early stages of the
particularly in the bile canaliculi
efferent veins (Figs. 108, 109); the
l tissues contain a significant and
number of neutrophilic polymor-
ar leukocytes in conjunction with
r elements ordinarily seen in viral
(Fig. 108). This additional histo-
ic feature of pericholangitis may
an atypical form of hepatitis, a
tion of the two conditions, or an
lent complication of hepatitis.

inary results of studies of a group
ases[37] have as yet not demonstrated
ific cause for this peculiar form of
It is not known whether an atypical
complicating bacterial organism, or
cal factors and conditions are re-
for this variant of hepatitis. To
m the available evidence, the clini-
e of the pericholangitic type of viral
is generally similar to that of regu-
of infectious hepatitis. The clinical
sually subsides eventually, with re-
normal values of laboratory tests
he normal histologic appearance of
tissue.

possible that there is a relationship
this type of atypical hepatitis and
olangiolitic" hepatitis and cirrhosis
described by Watson and Hoffbauer.[245] Follow-up studies of the cases of atypical hepatitis presently under observation may solve this problem.

"Hepatitis in the 'Neonatal Period.'" A form of hepatitis occurring in the neonatal period and clinically simulating biliary atresia was reported by Craig and Landing.[27]

These authors studied 20 infants, all exhibiting jaundice which first appeared shortly after birth.

The salient clinical findings are described in Chapter 23.

At operation, the biliary tree was found to be patent in all cases, and the liver was described as enlarged and soft, with a smooth bile-stained surface. In no case was there evidence of cirrhosis at operation. Icterus disappeared in 5 cases within 10 months and subsequently in one additional case. Of the 20 patients, 4 remained well from 1 to 10 years after discharge from the hospital; 12 died, 10 in their first illness and 2 after cirrhosis and portal obstruction had developed. Death occurred at ages varying from 5 weeks to 2¾ years. Four were not followed.

Postmortem examination showed a greatly enlarged liver, with a smooth bile-stained surface. The extrahepatic and intrahepatic bile ducts were patent. Histologically, the general architecture of the liver lobule was preserved, with portal triads and central veins in their usual places. The characteristic histopathologic feature of the disease at biopsy and autopsy was the presence of multinucleated, giant liver cells replacing most of the parenchyma. There was no evidence of formation of regenerative nodules of liver cells, and many of the lobules seemed to be smaller than normal because of loss of parenchymal tissue.

In their comments the authors compare the histologic appearance of the liver tissue in this condition with that in epidemic hepatitis. Except for lack of widespread central necrosis and absence of regenerative nodules, they emphasize the striking similarity between the two conditions. They mention the finding of bile droplets within the giant liver cells and suggest that their presence might be the result rather than the cause of jaundice.

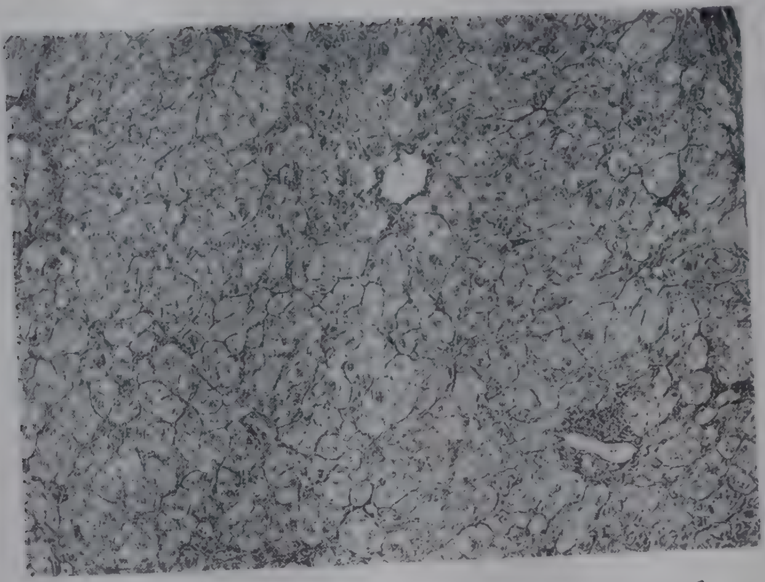


FIG. 110. Jaundice of the neonatal period. Congenital anomaly of liver cells and bile canaliculi. The liver lobules are taken up by multinucleated giant liver cells; the portal areas are small and lightly infiltrated with lymphocytes and monocytes; the efferent veins are in proper position. The sinusoids are greatly narrowed. × 50. (Armed Forces Institute of Pathology, Acc. 520738)

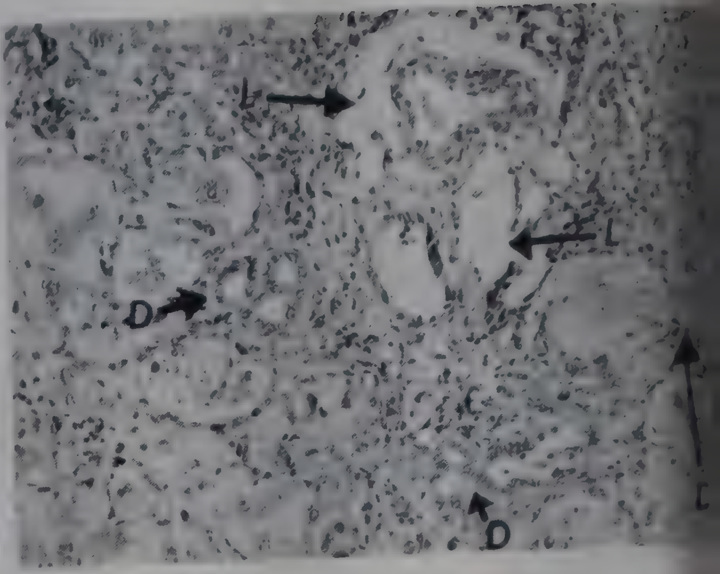


FIG. 112. Jaundice of the neonatal period. Congenital anomaly of liver cells and bile canaliculi. Portal canals show greatly enlarged lymph channels "L" and mild lymphocytic infiltrates. The bile ducts "D" are immature in nature; their lining cells are prominent, the lumina are irregular and devoid of bile; often their muscular coat is absent. × 160. (Armed Forces Institute of Pathology, Acc. 520738)

Preliminary studies of the cases belonging to this category[219] confirm the gross and the histologic features described by Craig and Landing[27] in most cases. In several other instances, however, a somewhat differ picture suggested that there might be seve histologic variants of this challenging c dition.

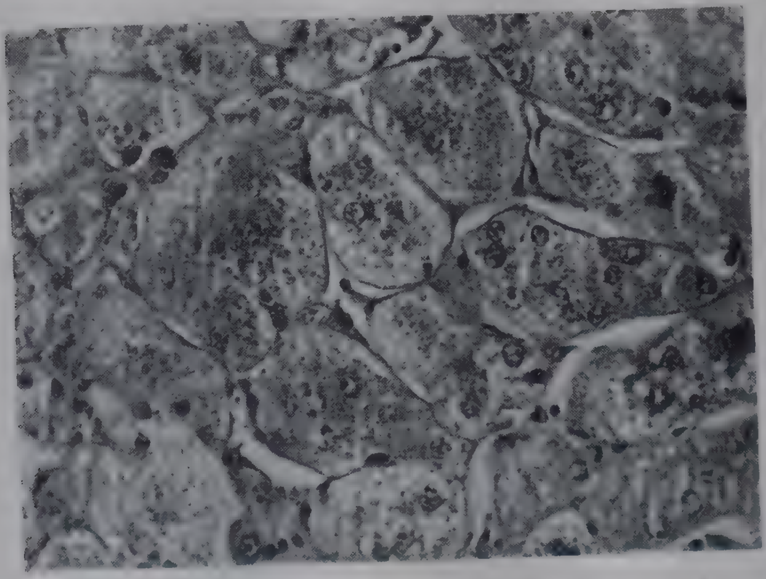


FIG. 111. Jaundice of the neonatal period. Congenital anomaly of liver cells and bile canaliculi. Giant liver cells, showing up to 20 nuclei and tiny bile particles in cytoplasm, occupy the entire width of the columns. Bile canaliculi are not visualized. The sinusoids are narrowed; some Kupffer cells contain bile pigment. × 360. (Armed Forces Institute of Pathology, Acc. 520738)

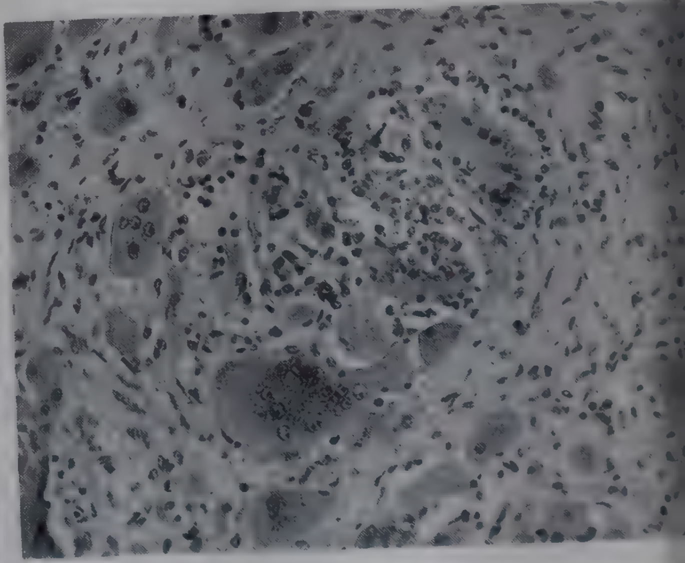


FIG. 113. Jaundice of the neonat period. Congenital anomaly of liver ce and bile canaliculi. Disintegration giant liver cells, with focal inflammato reaction composed of monocytes a polymorphonuclear leukocytes. × 2 (Armed Forces Institute of Patholo Acc. 561123)

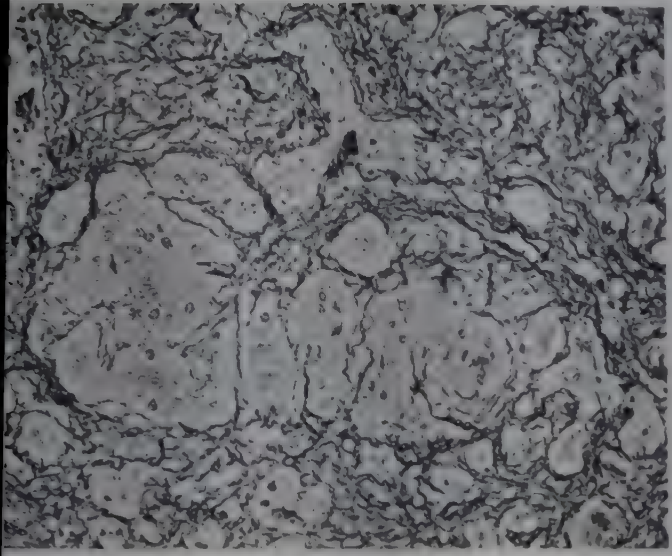


Fig. 114. Jaundice of the neonatal
iod. Congenital anomaly of liver cells
d bile canaliculi. Condensation of retic-
ım fibers about giant liver cells, pre-
nably because of disintegration of cells.
mpression of sinusoids by giant liver
ls. Wilder reticulum stain. × 185.
rmed Forces Institute of Pathology,
c. 525425)

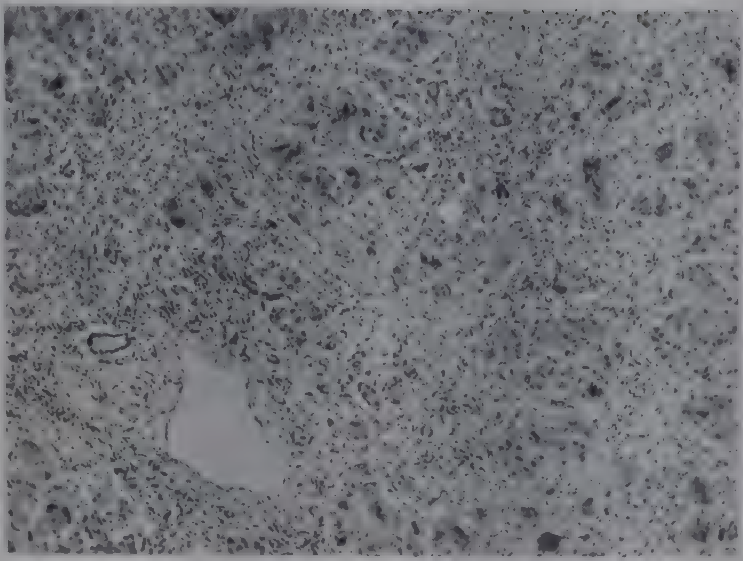


Fig. 115. Jaundice of the neonatal period. Congenital anomaly of liver cells and bile canaliculi. Diffuse scarring of liver with distortion of lobular architecture. Islands of multinucleated giant liver cells are surrounded by collapsed reticulum and collagenous fibrous tissue. Efferent veins are difficult to locate. The portal canals are of normal size and usually of normal configuration. Moderate infiltrates composed of lymphocytes, monocytes and polymorphonuclear leukocytes are scattered through the lobules. Nodules of regenerated liver cells are not recognized. × 75. (Armed Forces Institute of Pathology, Acc. 561123)

e most common type is characterized
mplete replacement of the other liver
by multinucleated giant liver cells but
ing the usual lobular arrangement
110). Other histopathologic features
are probably significant with regard
proper interpretation of this condition
s follows:

The multinucleated giant liver cells
y the entire width of the cellular col-
radiating from the efferent vein to the
ery of the lobule (Figs. 110, 111).

No intercellular bile canaliculi are vis-
d (Fig. 111) even in special prepara-
(Otami's stain for bile capillaries).

Tiny bile particles are seen within the
lasm of most of the giant liver cells,
ile is present in many of the Kupffer
(Fig. 111).

The interlobular bile ducts are free of
and in some cases these ducts appear
of immature nature (Fig. 112).

There is no histologic evidence of an
diate functional relationship between
ile-containing giant liver cells and the
obular bile ducts (Figs. 111, 112).

In some cases iron pigment can be
nstrated in Kupffer cells.

The portal canals in many instances
are rather small and sometimes show distention of lymphatics (Fig. 112); occasional portal areas are devoid of intralobular bile ducts.

8. Accumulation of bile particles in giant liver cells seems to lead to damage and eventual destruction of these elements (Fig. 113).

9. Destroyed liver giant cells apparently are not regenerated, and the reticulum fibers formerly associated with these cells become condensed due to collapse of the tissue (Fig. 114).

10. The final effect of the giant-cell transformation of the neonatal liver is one of postnecrotic collapse and cirrhosis (Fig. 115), resulting in hepatic insufficiency.

Other histologic types seen in cases presenting a clinical picture similar to that of giant-cell transformation of the neonatal liver show certain abnormalities in the development of small bile ducts and bile canaliculi, as well as in the relationship of these structures to liver cells. However, these types must be studied in greater detail before their histogenesis can be interpreted.

Although multinucleated giant liver cells can be seen occasionally in cases of acute viral epidemic hepatitis, particularly when characterized by active regeneration, the histologic pictures of the two conditions have little in common. Most of the features characteristic of acute viral hepatitis occurring in postnatal life—formation of balloon cells, acidophilic elements, necrosis of individual liver cells, followed by mitotic and amitotic regeneration and restoration of damaged and necrotic cells, disarray of the lobular structure—generally are missing; the massive portal infiltrates composed of monocytes and eosinophils, as well as the intralobular infiltrations, are either scantily developed or are lacking altogether in "hepatitis of the neonatal period"; the intact argentophilic stroma seen in the uncomplicated cases of viral hepatitis contrast with the marked duplication and condensation of reticulum fibers about giant liver cells. Ordinarily, lipofuscin is not identified in the giant liver cells nor is it seen in Kupffer cells; however, its presence may be masked by bile. The iron pigment in the Kupffer cells may be related to blood destruction. While the presence of multiple tiny droplets of bile in the giant liver cells is characteristic of "neonatal hepatitis," this feature is very uncommon in viral hepatitis, even though bile often can be seen in Kupffer cells and is sometimes conspicuous in intercellular bile capillaries. Apparent increase in the number of small bile ducts in portal areas, as seen in cases of persistent viral hepatitis, is not a feature in "neonatal hepatitis." Bile canaliculi, which ordinarily run a zigzag course between adjacent liver cells in the center of the columns, are either missing or sometimes can be demonstrated only near the portal canals.

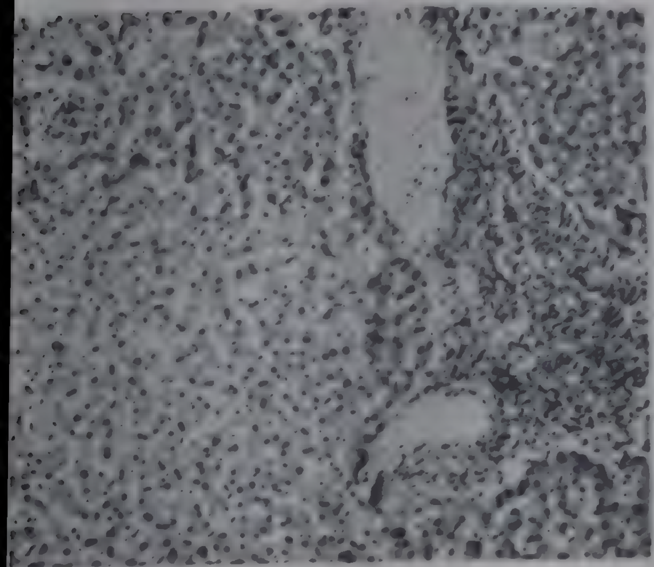
The columns composed of giant liver cells seem to lack connection with the efferent biliary passages so that bile cannot be delivered from the liver cells through the canaliculi into the bile ducts. However, since bile formation apparently is not impaired, the accumulated bile is retained within the giant cells, causing damage, degeneration and even necrosis.

It is difficult to state whether the m
nucleated giant cells constitute an aty
reaction to injury or are malformed
cells. It should be emphasized that it is
number and the nature of these cells
distinguish this lesion from the viral hep
of postnatal life, including cases occurri
children between birth and 14 years
age.[189] For this reason evidence of the i
tity of "neonatal hepatitis" and viral he
tis present in postnatal life is rather ten
unless it is assumed that the reaction o
liver tissue to the virus in intra-uterine
is entirely different from that in postn
life. From the available evidence it ca
be denied that a virus infection could c
such an alteration.

Although the histopathologic cha
seen in "neonatal hepatitis" are certain
the result of atresia of the larger bile
sages, they do seem to be related to a la
communication between the bile-for
and the bile-delivering apparatus of the
Whether this is a congenital abnormali
the effect of a damaging infectious age
the embryonal liver cannot be stated.

A possible relationship between
hepatitis in the mother during pregnanc
the "hepatitis in the neonatal period"
infant had been suggested previousl
Stokes et al.[228] in their report of a ser
such cases. This assumption was bas
part on the successful transmission to h
volunteers of the virus of serum he
from one of the infants and its m
Later, Dible[33] reported a series of 4
which he attributed to viral hepatitis.
ever, Martini,[150] in reporting a series
cases of viral hepatitis occurring in m
during pregnancy, states that transmis
the virus to the fetus could not be
with certainty. Since the virus of serum
titis can be demonstrated sometimes
sons with no history of present or pa
hepatitis,[225] the lack of disease in the
does not rule out the possibility of
placental transmission of the virus
infant. Does the presence of the virus
however, constitute proof of the exis
hepatitis?

The histopathologic picture obse
a group of such cases from the
Registry is interpreted as resulting



ig. 116. Infectious mononucleosis. portal and intralobular infiltrates isting of atypical lymphocytes. Iden- cells also are seen in the sinusoids. liver cells are uniform and in normal ngement. × 120. (Armed Forces In- te of Pathology, Acc. 151166)

of development of bile canaliculi, a mation of as yet undetermined y.

HISTOPATHOLOGIC IFFERENTIATION OF VIRAL HEPATITIS FROM OTHER CONDITIONS

only disease which histologically re- s viral hepatitis is infectious mono- sis, in which infiltrates of atypical ocytes occur in portal canals and the lobules (Fig. 116). A positive ne of the heterophil antibody test has eported in about one third of the cases al hepatitis,[40] but apparently absorp- rocedures have shown such results to se.[84] It goes without saying that the ulations of cells in the liver in cases ectious mononucleosis are the inci- result of the circulation of an in- d number of atypical lymphocytes in ood.

netimes focal necrosis secondary to ous processes may mimic the focal sis of liver cells of acute hepatitis. ver, in most of these instances the re- cells are predominantly polymorpho- r leukocytes, and all other features of hepatitis are lacking.

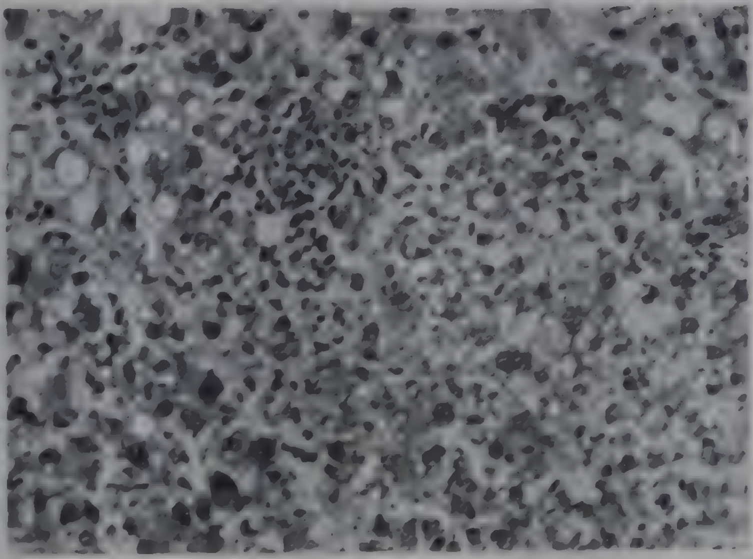


Fig. 117. Yellow fever; death 10 days after onset of disease. Focal necroses, accompanied by infiltrates composed of polymorphonuclear leukocytes, lymphocytes and monocytes. Many of the liver cells show degenerative changes with vacuolization, and a few Councilman bodies are present. × 275. (Armed Forces Institute of Pathology, Acc. 275608)

In passing, the artefacts seen in tissues removed by surgical means may be mentioned.[115] Such lesions should not be confused with those seen in viral hepatitis.

In the stage of acute necrosis of liver cells during the development of portal cirrhosis, the presence of Mallory bodies, surrounded by inflammatory cells, is perhaps remotely

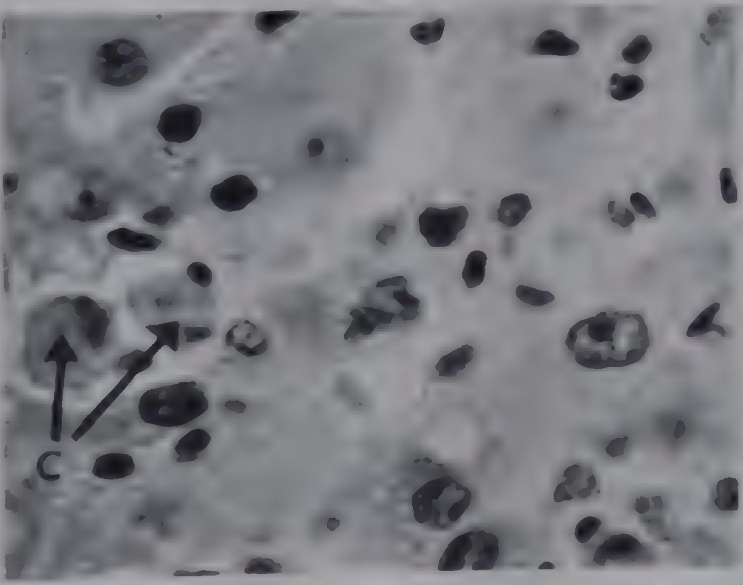


Fig. 118. Yellow fever. Degenerative changes in liver cells with vacuolization. Several Councilman bodies at "C." × 980. (Armed Forces Institute of Pathology, Acc. 488712)

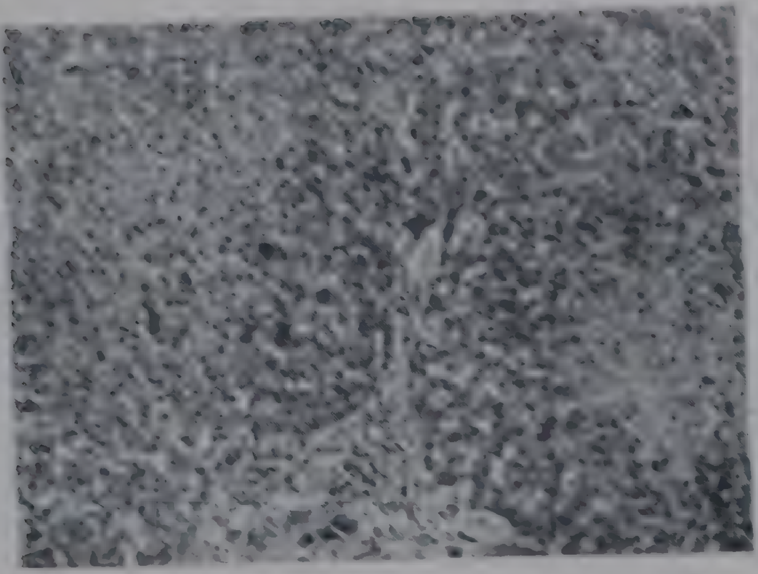


FIG. 119. Canine hepatitis. Areas of necrosis of liver cells in central portion of liver lobules. Moderate irregularity of liver cells. Scanty monocytic infiltrates in portal canals and in lobular parenchyma. Moderate congestion of sinusoids. × 125. (Armed Forces Institute of Pathology, Acc. 198762)

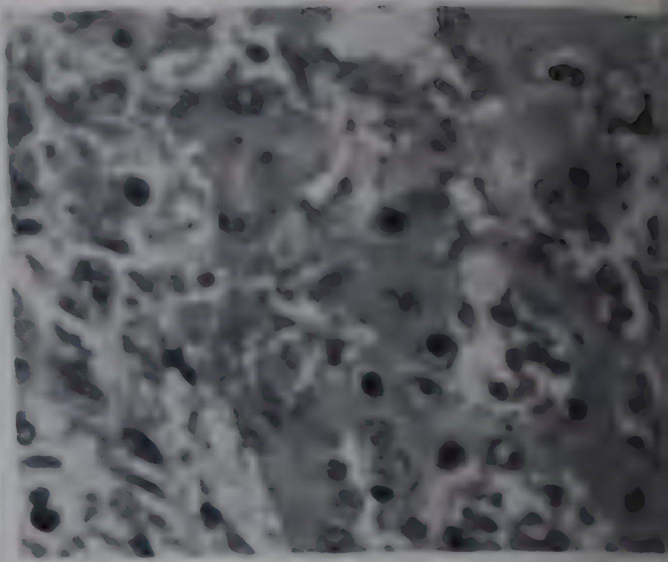


FIG. 120. Canine hepatitis. Intra clear inclusions in liver cells. × (Armed Forces Institute of Patho Acc. 198762)

reminiscent of features seen in viral hepatitis.

The possibility that viral hepatitis may complicate portal cirrhosis has been suggested. Although it cannot be denied, no proved instance of such a complication has been observed in the material of the Registry of Hepatic Pathology.

The Councilman bodies present in yellow fever may bear some resemblance to the acidophilic elements of viral hepatitis. However, most of these bodies are vacuolated, thereby contrasting with the rather homogenous hyaline transformation of liver cells in hepatitis (Figs. 117, 118). The regional necrosis of liver cells in yellow fever, the fatty metamorphosis, coupled with a divergent clinical history, will separate the two conditions easily in most cases.

Sometimes granulomata of various etiology and types may mimic focal necrosis; but their predominant presence in portal areas and their different cellular composition will serve to distinguish them from lesions of hepatitis.

There are several conditions which clinically and, to some extent, pathologically resemble the fatal and fulminant type of hepatitis. Mushroom poisoning, arsenic,[201, 202, 209] phosphorus,[91] and chloroform[249] poisoning and eclampsia have been found to imitate acute yellow or red atroph cally, it is often impossible to differe between these conditions without the tory, especially in sporadic hepatitis the pathologic differentiation may be cult at times, particularly in later when regeneration, collapse and s confuse the picture. However, poisonin ally produces intense fatty change early phase, and eclampsia is charact by hemorrhages and necrosis.

Many unsuccessful attempts have made in the Registry of Hepatic Pa to detect "serous hepatitis"[194] in biop terial, particularly in the early stage o viral hepatitis. Although material sug protein precipitate in the problema of Disse is seen commonly in post material of fatal viral hepatitis and conditions, it is not visualized in w served and properly fixed biopsy m Extensive studies and countless obser of the relationship between liver ce the reticular stroma point toward an and intravitally inseparable contact the cellular and the structural e thereby throwing doubt on the exis the space of Disse.

INFECTIOUS HEPATITIS OCCU IN THE ANIMAL KINGDO

HEPATITIS CONTAGIOSA CAN

A well-known infectious disease

curs with significant frequency in ts of the world, hepatitis contagiosa been the subject of extensive clini- atory and etiologic studies.[23, 24, 108, 200] Although young dogs of all re susceptible, the disease is most in terriers. The clinical picture is by fever and apathy, often accom- diarrhea and vomiting; during the e, convulsions may occur. At post- examination the liver is described as nd light in color with edema of the patis, the gallbladder and of the mph nodes. The peritoneal cavity ntains albuminous fluid which is lly hemorrhagic. The spleen is en- nd congested, as are the lymph he tissues of the mediastinum and ntery are also edematous. The right ne heart may be dilated. The brain anemic and edematous.

ogically, the liver is described as centrolobular necrosis, sometimes the whole lobule, edema and effu- lood into the spaces of Disse, and changes manifested by eosin- egeneration, necrobiotic nuclear al- and breaking up of the cytoplasm nce of an apparently intact nucleus 9). Intralobular and portal infil- nsist of leukocytes and monocytes. nal organs may show congestion, nd regressive changes, with hemor- nd infiltrations. The brain often ex- opial serous effusions, minor hemor- into the parenchyma and lytic ation. Sometimes there is meningo- itis of nonpurulent character.

iver cells, Kupffer cells and endo- ells in most of the parenchymatous nd in other situations contain intra- nclusions which are amphoteric and ositive Feulgen reaction (Fig. 120). clusions usually are associated with e changes in the organs.

isease can be diagnosed by comple- ation tests, and the antigen is always n livers containing the characteristic bodies. Specific antibodies can be in the blood stream after experi- nfection produced by parenteral in- f bacteria-free filtrates. It is assumed condition is the result of a virus , and it has been suggested that the infectious agent is related to the virus of fox encephalitis.[64]

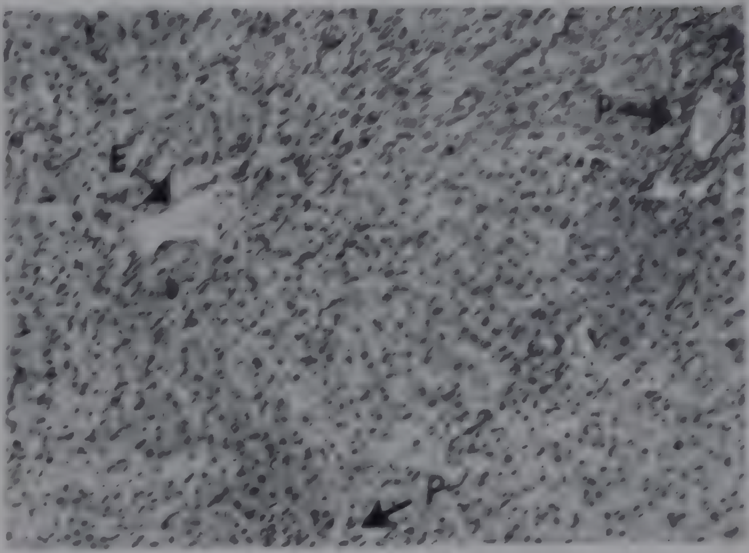


FIG. 121. Liver of a horse, case of "X" disease. Necrosis of liver cells of almost the entire lobule, leaving only small islets of liver cells in the peripheral portion of the lobule, particularly about the portal canals ("P"). Lipofuscin in phagocytes about efferent veins ("E"). × 130. (Armed Forces Institute of Pathology, Acc. 319)

PORCINE HEPATITIS

According to Andersen,[2] porcine hepatitis occurs both sporadically and in epidemics and is characterized by jaundice and parenchymatous degeneration of the liver. The epidemiologic pattern of this disease apparently is similar to that of human infectious hepatitis, and the author believes that the epidemic jaundice of pigs and the infectious hepatitis of man are due to the same etiologic agent. Transfer of this disease from man to pig was accomplished reportedly by materials from the duodenum of a patient suffering from infectious hepatitis.

The histologic changes in the liver consist of swelling of liver cells with granularity and vacuolization of the cytoplasm but apparently unaltered nuclei. The pattern of the liver-cell columns is obscured, and the capillaries are collapsed. No increase in connective tissue is apparent.

To judge from the illustrations and from the description, the histopathologic changes in the liver in porcine hepatitis cannot be considered as identical with those seen in human infectious hepatitis.

Acute Liver Atrophy in Horses

Theiler[284] has described a disease among horses in South Africa referred to as "staggers" or "malziekte," generally corresponding to acute liver atrophy in man. "Staggers" was observed first in horses that had passed through a horse-sickness experiment, and at the time it was thought to be connected with the immunization.

The mortality rate after inoculation with identical material varied from 2 to 18 per cent, depending on the treatment of the animals after inoculation. Horses that were not used for work of any kind for some weeks after the inoculation had a low morbidity and mortality, while the rates were high among those used for work and exposed to all climatic influences.

Clinically, the course of the disease is very rapid, usually about 24 hours, but fatal cases of shorter duration—even less than 6 hours—have been reported. Among the prodromal symptoms mentioned are sluggishness, unsteadiness of gait and tendency to stumble. While in the stable, the horses are listless and dull; they do not feed and they hang their heads. The scleras may be jaundiced. Body temperature is likely to be subnormal. The horses soon have difficulty in standing, they lean against the wall in a semiconscious state and eventually collapse. The skin becomes abraded because the animals lean so heavily against the rough surfaces of the stall. Finally, they slip and go down, rolling over on one side. Occasionally, a horse will have "fits," knocking its head against the wall; when taken into the paddock, it moves about aimlessly, sometimes in a circle, until it falls. Finally, coma overtakes it. Sometimes dyspnea is present. Symptoms related to the central nervous system vary from somnambulance to semiconscious states, opisthotonos and yawning.

At autopsy of the animals, jaundice was generally present. Hydrothorax and ascites were uncommon, but sometimes hydropericardium was observed. The retropharyngeal, the pleural, the mediastinal and the bronchial lymph nodes were edematous, hyperemic and even hemorrhagic. The myocardium showed cloudy swelling, and petechiae were seen in the endocardium. The lungs were hyperemic and edematous with frothy fluid in the trachea. The spleen showed specific changes, but hyperemia and atro were noted in individual cases. The li tended to be smaller than usual, and edges were smooth and flattened. The c sule was either smooth or partly shrivel The consistency of the parenchyma usually firm, more rarely soft and britt color varied from light brown to light yell and was rarely dark. The centers of the l ules were grossly dark and sunken, rounded by grayish meshes. The kidn showed a yellowish opaque discoloration the cortex and hyperemia of the parenchy The urine in the bladder was freque brown tinged and even hemoglobin-stain petechiae could be seen in the mucosa. casionally, the brain appeared to be anen

Microscopically, the changes in the li consisted of necrosis of liver cells in center of the lobules, with few if any in liver cells in the periphery. Frequently, liver cells could be recognized, and former parenchyma was replaced by a mogeneous substance, full of a yellow ment and containing endothelial cells white blood cells. The efferent veins and central sinusoids were distended with bl The relatively preserved liver cells conta large fat globules. There was active re eration of liver cells, with formation of cells and presence of budding bile d The round-cell infiltrations of the lym cytic type were seen most frequently in septa. A large amount of yellowish b pigment was present both inside and ou of the liver cells and in endothelial Some of the pigment gave a positive reaction, but most of it could not be r nized as bile pigment (by the Gmelin even though a general state of jaundic present in all cases. A slight cirrhotic tion was noticed in some instances; how this was considered to be coincidenta not connected with the disease.

The cause of the acute liver atrophy horses remains undetermined. Attem transmit the disease from affected anim other horses were unsuccessful, and the of the acute liver atrophy of horses r as yet undetermined. Thieler suspect the ingestion of a toxic plant (*senec folius*) is the primary cause of horse-s vironmental influences as contributors.

utbreak of a "secondary disease" isease) in horses, resembling acute rophy and occurring subsequent to ion of infectious equine encephelo- antiserum, was reported by [7, 148] (Fig. 121).

ost of these cases the disease de- from 30 to 90 days following the tration of antiserum, combinations of d serum, or vaccine. These instances titis and jaundice incidental to imion of horses are indeed reminiscent reaks of homologous serum hepatitis g the use of antisera and inocula in [7, 49, 55, 83, 106, 135, 176, 206, 221, 227, 233]

r, all attempts to produce the disease entally by inoculation of laboratory , including horses, with tissues from clinical or recovered cases, have been ssful.[211]

FECTIOUS HEPATITIS OCCURRING IN DUCKS

é and Ratcliffe[134] have described an us hepatitis occurring naturally in which is transmissible to other ducks cklings. The lesions observed in the e said to resemble those of human patitis.

AVIAN MONOCYTOSIS

lesions seen in the liver of fowl in monocytosis[113] (so-called pullet disppear to be an expression of a general n rather than of a primary viral s.

CONCLUSIONS

he many different histopathologic exns seen in human viral hepatitis reprely facets of the same disease brought by differences in severity, extent and duration of the process. In the fulminant type, necrosis of liver cells occurs suddenly and affects most of the parenchyma, causing death within a short time. In the nonfatal kind the essential nature of the process is shown in slow motion, revealing degeneration and destruction of individual liver cells accompanied by monocytic intralobular and periportal infiltrates, and followed by regeneration of liver tissue with eventual restoration. Between the two extremes lie cases of persistent hepatitis characterized by recurring focal lesions, the state of postnecrotic collapse and of coarse lobular cirrhosis. These latter two conditions are thought to be the result of simultaneous destruction of confluent groups of liver cells, followed by collapse of the stroma and by regeneration of parenchyma from surviving cell elements. In coarse nodular cirrhosis subtotal necrosis of liver tissue is followed by formation of hyperplastic nodules composed of reorganized groups of regenerated liver lobules, separated by septa, containing "proliferating" bile ducts, which represent the collapsed and condensed former reticulum and periportal fibrous tissue.

2. The anicteric and the pericholangitic forms of hepatitis are probably atypical variants of viral hepatitis. The anicteric form is poorly understood. The pericholangitic form is complicated by intrahepatic retention of bile, particularly in bile capillaries about efferent veins, apparently the result of partial obstruction of the biliary channels by an inflammatory reaction of undetermined origin in the stroma of the portal canals.

3. The "'hepatitis' occurring in the neonatal period" is interpreted as the result of a congenital anomaly of undetermined etiology, characterized by a failure of development of intercellular bile canaliculi.

4. Hepatitis in the animal kingdom has some clinical and pathologic features in common with human viral hepatitis but does not seem to be identical.

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Chapter 11 VIRAL HEPATITIS

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DEFINITION

The term "viral hepatitis" will be used for reference to those forms of hepatitis that are caused by two or more hepatotropic, filtrable, infectious agents not yet identifiable by specific serologic or cultural methods, which produce systemic disease in which a characteristic type of liver injury is the outstanding result of human infection. As such, the syndrome of "viral hepatitis" includes infectious or infective hepatitis, "catarrhal" jaundice, epidemic hepatitis or jaundice, homologous serum hepatitis or jaundice, post-transfusion hepatitis, postvaccinal hepatitis and postinoculation or syringe hepatitis.

ETIOLOGY

The etiologic agents responsible for the syndromes of hepatitis under consideration have many properties that justify their tentative classification as viruses.[29, 46, 54, 56] A variety of observations indicate that the hepatitis viruses possess a high degree of resistance to many agents or conditions that inhibit or destroy most other infectious agents. Hepatitis agents have not yet been identified microscopically or by cultural or serologic methods, and *confirmed* evidence of their propagation in laboratory species other than man unfortunately has not been obtained in spite of intensive efforts.[26, 29, 34, 45, 83, 90] As man continues to be the only proved susceptible species to date, most of the advances in knowledge concerning these agents have been the result of studies carried out in human volunteers during the past 15 years.

Epidemiologic observations[23] and studies
in human volunteers[29, 46, 54] provide stror
evidence that at least two agents are co
cerned. The exact relationship between the
two viruses, whether different viruses
different strains of the same virus, remai
to be determined. For purposes of refe
ence, the broad terms "Virus IH" and "Vir
SH" are suggested as a tentative aid in avoi
ing the confusion resulting from the lack
specific methods for identification of t
viruses concerned.[56] As "Virus IH" ar
"Virus SH" each may include one or mo
strains with similar properties, these tern
are considered by the author as preferable
the more specific and singular implicatio
suggested by the terms "Virus A" ar
"Virus B"[46, 90] which have been suggeste
subsequently by others for reference
"Virus IH" and "Virus SH" respectively. F
the same reason, when characteristic ep
demiologic or human volunteer data are n
available concerning one of the hepati
agents, as often is the case in clinical pra
tice, the broad term of "viral hepatitis" a
pears to be preferable.

"Virus IH" (Virus A) has been identifi
primarily with the clinical and epidemi
logic syndrome of infectious (epidemi
hepatitis which occurs spontaneously in
form of sporadic cases or epidemics in as
ciation with an incubation period vary
from 2 to 6 weeks. "Virus SH" (Virus
has been associated with the syndrome
hepatitis that characteristically develops fr
1½ to 6 months after the occurrence of
opportunity for parenteral entry of the vir
The epidemiologic term "homologous ser
hepatitis" unfortunately has acquired a m
leading etiologic implication in that it usua
has been employed for reference to
hepatitis syndrome occurring after the l

TABLE 23. OBSERVED DIFFERENCES BETWEEN TWO HEPATITIS VIRUSES

URCE	OBSERVATION	VIRUS IH (OR A)	VIRUS SH (OR B)
	1. Usual type of onset	Abrupt; febrile, often high fever; occasionally one chill	Insidious; afebrile or temperature usually less than 100°; rarely a chill
ved in man Vol- eers With perimen- y Induced ections	2. Abnormal hepatic tests	Preceded by symptoms for several or more days	Often precede symptoms by several to many days
	3. Thymol and colloidal gold responses	Usually abnormal	Frequently negative or only weakly positive
	4. Usual incubation period (virus entry to clinical onset)	2 to 6 *weeks*	1½ to 6 *months*
	5. Route of inoculation	Clinical hepatitis follows either oral or parenteral entry after 2 to 6 weeks	Clinical hepatitis after parenteral *but not* after *oral* entry
	6. Virus demonstrated in:	Blood and feces	Blood only
	7. (A) Oral ingestion of known infectious serum	Clinical hepatitis	No hepatitis
	(B) Parenteral injection of infectious serum	Clinical hepatitis	Clinical hepatitis
	8. Oral ingestion of feces suspensions	Clinical hepatitis	No hepatitis
	9. Resistance to infection (immunity after):		
	(A) Virus IH infection	Present	Absent
	(B) Virus SH infection	Absent	Present for at least 1 year
l on Epi- miologic dies	10. Incidence after 30 years of age	Sharp decrease	No apparent decrease
	11. Prevention by prophylactic injections of gamma globulin (human, ethanol p'pt.)	Yes	No

to 6 months interval. It is *emphasized*
“Virus IH” also may be transmitted by
od or its products and cause “homologous
m hepatitis” after an interval varying be-
en 2 weeks and 2 months. Thus syn-
mes of hepatitis occurring from 2 weeks
months after exposure to blood or its
ducts may be of viral origin and could
ifiably be called “homologous serum
atitis.”

lthough the properties of the two hepatitis viruses described above appear to account satisfactorily for most of the viral hepatitis syndromes ordinarily encountered, the possibility remains that other similar strains of hepatitis virus exist. The field epidemiologic studies[23] and the experimental studies in human volunteers[29, 46, 47, 54] that have provided the basis for the distinction between “Virus IH (A)” and “Virus SH (B)” are summarized in Table 23 at the top of this page.

EPIDEMIOLOGY

A tentative working concept of the etiology and the epidemiology of viral hepatitis, based on available information, is presented in Figure 122.[58] Human blood and feces are the only proved sources of hepatitis virus, and the agents may be present in these materials in very high concentration. Thus, 50 cc. of a 1:1,000,000 dilution of whole blood has been shown to be infectious.[18] The viruses apparently may be present in blood or feces in the absence of previous or existing symptoms or signs, and the blood or the feces may be infectious before, during, or after the occurrence of a clinical illness recognizable as hepatitis.[29, 56] The existence of long-term asymptomatic blood or feces carriers of hepatitis virus with no history of recognized hepatitis has been definitely established recently.[52, 64, 83] As no host of hepatitis viruses other than man has been recognized, the current concept of epidemiology thus begins and ends with the human host. Either of the recognized viruses may be acquired from human blood, but only "Virus IH" has been proved to be present in the feces. Neither has been proved to be pres in the urine or the nasopharyngeal secretio Most of the naturally acquired infectio sporadic or epidemic, appear to be due "Virus IH" transmitted by the intestinal-o route by one of the various mechanis shown in Figure 122. The possible mech nisms of transfer of either of the hepat viruses from human blood or its derivati also shown in Figure 122, are multiple. Th include transfusion or other injection of h man blood, plasma, or serum (or from n terials containing or prepared from th substances) and infection from imprope sterilized syringes, needles, lancets, or oth instruments that have been in contact w human blood. Recently, evidence of in-ut transmission from an apparently heal carrier mother to her fetus has been c tained.[84]

With the development, by Cohn and workers,[14] of technics for the fractio tion of the human plasma proteins by ethanol precipitation method, and with widespread clinical use of the blood fr tions thus produced, the question of wheth or not these fractions might transmit vi

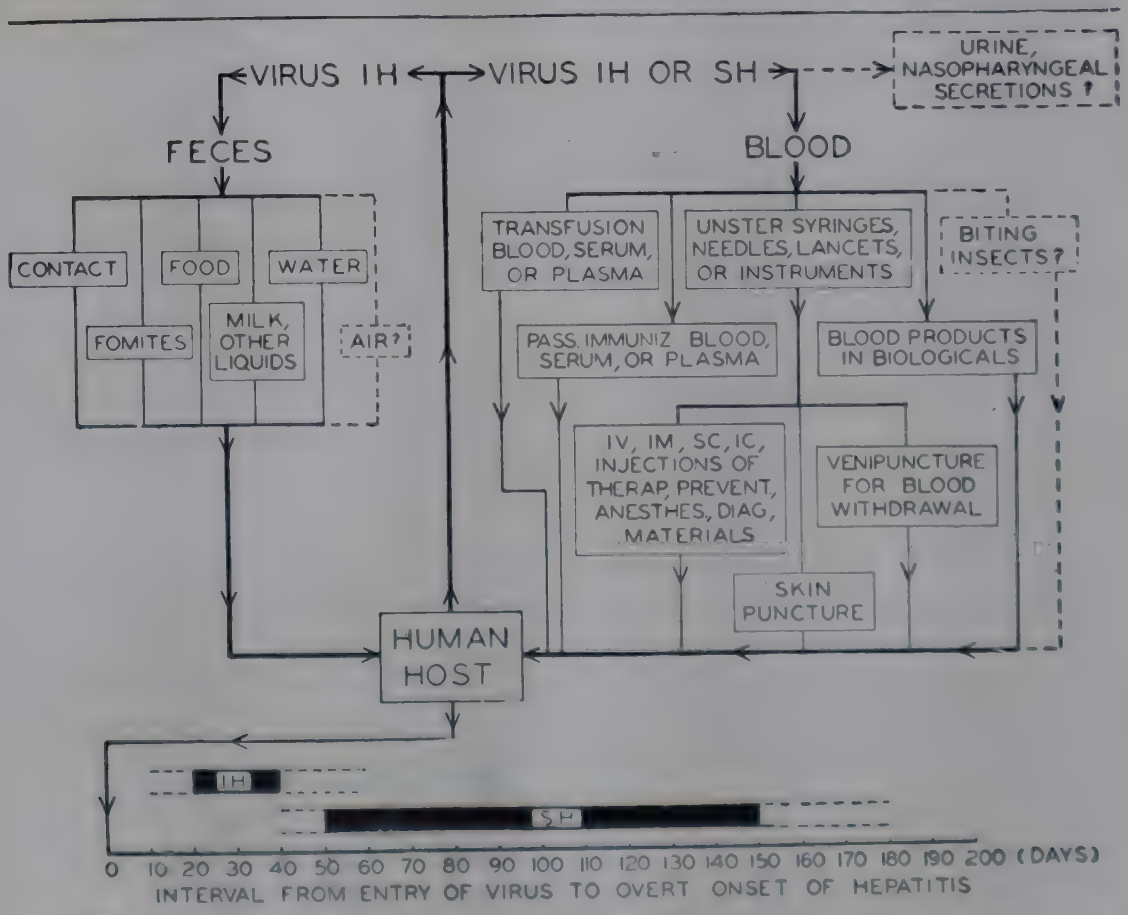
VIRUS IH
VIRUS IH OR SH
URINE, NASOPHARYNGEAL SECRETIONS ?
FECES
BLOOD
CONTACT
FOOD
WATER
FOMITES
MILK, OTHER LIQUIDS
AIR ?
TRANSFUSION BLOOD, SERUM, OR PLASMA
UNSTER SYRINGES, NEEDLES, LANCETS, OR INSTRUMENTS
BITING INSECTS ?
PASS. IMMUNIZ. BLOOD, SERUM, OR PLASMA
BLOOD PRODUCTS IN BIOLOGICALS
IV, IM, SC, IC, INJECTIONS OF THERAP, PREVENT, ANESTHES, DIAG, MATERIALS
VENIPUNCTURE FOR BLOOD WITHDRAWAL
SKIN PUNCTURE
HUMAN HOST
IH
SH
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 (DAYS)
INTERVAL FROM ENTRY OF VIRUS TO OVERT ONSET OF HEPATITIS

FIG. 122. Concept of the etiology and the epidemiology of viral hepatitis. (Neefe, J. R.: New England J. Med. **240**:445)

is has assumed great importance. *amma globulin fraction,* as prepared hyl alcohol (ethanol) precipitation, s to be free of hepatitis virus, despite t that individual lots of gamma glob- human immune serum globulin) may ent the pooled plasma of thousands nors.[56, 82, 83] It would appear that, in reparation of this fraction by ethyl l, the virus is inactivated, eliminated, utralized. The *albumin fraction* pre- in this way, after appropriate heating, t been shown to contain the virus; the in solutions, as now prepared, are ap- tly safe, due to the fact that this prod- n withstand the degree of heating re- l to inactivate the virus.[24, 67] Viral hep- likewise has not been reported follow- e use of *antihemophilic globulin,* as red by the ethyl alcohol precipitation d.[72] The *disease has occurred,* how- following the use of *topical thrombin.*[72] st be emphasized that the above ob- ions apply only to the fractions pro- by the ethanol precipitation method, hat fractions resulting from other meth- f preparation will require re-evaluation hould not be regarded automatically as

e disease now has been recognized as cupational disease among professional nnel and laboratory workers[37, 48, 86] en- in the handling of blood or its products and the extent of this hazard has been nized further by the recent demonstra- of virus in the blood of apparently y persons.[64, 84] Although there is no te evidence of mechanical or biologic nission of hepatitis virus by biting in- this possibility must exist whenever an gic agent may be transmitted by minute nts of plasma or blood. The many po- l mechanisms for acquiring hepatitis from either blood or feces of either usly infected or apparently healthy ns clearly indicate that a history of ct with an overt case of hepatitis is of importance as a factor for or against iagnosis of viral hepatitis in any sus- d case.

ailable reports indicate that "Virus IH" ably is world-wide in distribution. The raphic distribution of "Virus SH" is less well defined, although available evidence suggests that it, too, is widespread.

"Virus IH" hepatitis occurs in the sporadic or epidemic form at any time of the year, although epidemics tend to occur more frequently during the fall, early winter and spring.[23, 47, 69] *Epidemics* usually occur under conditions which favor crowding and deterioration of general sanitation and personal hygiene. Such conditions are prevalent in times of war; in peacetime they are encountered most frequently in camps, institutions and within certain family units. Gauld states that the typical and most frequently occurring type of epidemic is not explosive in nature but rather runs a leisurely course, taking from 3 to 4 months to spread through a given population. In this type, the epidemic is likely to begin with an initial case followed by single, or sometimes several, additional cases occurring at intervals of 1 to 3 weeks. This also is the typical course of outbreaks within families. In addition to this common type of epidemic pattern, epidemics have been reported in which the onset was more explosive, and the subsequent course of the epidemic was more rapid. This pattern is characteristic of that usually noted with mass infection from a common source, for example, by contaminated drinking water.[22, 25, 53]

"Virus SH" infections, as indicated by the artificial method of transmission, would not be expected to have a seasonable influence unless future evidence should indicate that biting insects are a factor.

Both sexes and all races are susceptible to both of the recognized hepatitis viruses. In civilian populations, "Virus IH" hepatitis occurs predominantly in children and young adults but may occur at any age. However, a sharp decrease in incidence is observed in exposed persons over the age of 30, presumably due to acquired immunity. There apparently is no decrease in susceptibility to "Virus SH" infections with advancing age. In fact, this disease probably occurs more frequently in adults because of their more frequent exposure to the mechanisms of transfer of hepatitis virus from blood and its derivatives. Exact incidence figures are not available for either virus, although the disease now is reportable in many states. The actual incidence undoubtedly is much greater than that reported because of the frequent lack of recognition of nonicteric cases which may account for as many as 70 per cent of the actual infections.[5, 59, 84] The nonicteric form may be the rule in young children, and such unrecognized cases undoubtedly constitute an important source of infection.[10, 11] Epidemics of hepatitis occur annually in both civilian and military groups. In the Armed Forces of this country, acute hepatitis continues to be one of the important medical problems and causes of man-days lost from duty per year.

The usual incubation period of "Virus IH" hepatitis apparently ranges from 2 to 6 weeks *irrespective of whether the route of entry is oral or parenteral.* Under certain conditions, particularly circumstances leading to attenuation, the incubation period may be prolonged considerably.[53] The interval between parenteral entry of "Virus SH" and the onset of clinically recognizable manifestations usually ranges from 1½ to 6 months.

IMMUNITY

The available data indicate that infection with either "Virus IH" or "Virus SH" apparently is followed by resistance to reinfection with the homologous virus.[23, 29, 54] Although the duration of such resistance has been demonstrated experimentally only for a period slightly longer than one year, epidemiologic and other data suggest that the duration of resistance to reinfection with "Virus IH" may be lifelong and similar to that resulting from measles. This is further supported by the protective effect against "Virus IH" infections of human immune serum (gamma) globulin prepared by the ethanol fractionation method from the pooled plasma of human adults.[82, 83] The effectiveness of this material in this respect suggests that many persons must have had previous inapparent immunizing infections. Epidemiologic data regarding immunity from "Virus SH" infections beyond the period of one year are not available. Available information suggests that this virus may be associated with a peculiar immunologic response, as human immune serum globulin and convalescent plasma obtained after "Virus SH" infections have failed to protect human volunteers from "Virus SH" infections.[7] In ad tion, a difference in the globulin respons to infection with the two viruses is suggeste by the fact that, under experimental cond tions in limited numbers of human volun teers, "Virus IH" infections uniformly we associated with strongly positive thymol, co loidal gold and zinc turbidity reaction whereas "Virus SH" infections frequentl were associated with negative respons with all of these tests throughout the cour of the infection.[55, 56]

Although the evidence seems to be cle that considerable resistance to reinfectio with the same virus exists for one or mo years after infections with either "Virus IH or "Virus SH," the evidence seems to equally clear that no cross immunity b tween the two viruses exists.[23, 29, 54] In fac certain epidemiologic data suggest that, wh equally exposed to one virus (IH or SH those previously infected with the other vir have a somewhat higher incidence of infe tion than those without recognized previo infection with the other virus.[23]

Although suggestive results with skin tes and complement-fixation tests have been o tained,[26, 29, 33] the results have been inco sistent, and attempts at confirmation others have been unsuccessful to date. Th reliable methods of this type are not available for clinical use.

TABLE 24. RESULTS THAT MAY BE OBTAIN THEORETICALLY BY INJECTION OF BLOOD FRO PATIENTS WITH VIREMIA (IH OR A; SH OR

VIRUS IN DONOR'S BLOOD	IMMUNE STATE OF RECIPIENT	RESULT
A (IH)	O	Short incubatio
A (IH)	B	Short incubatio
A (IH)	A	No disease
B (SH)	O	Long incubatio
B (SH)	A	Long incubatio
B (SH)	B	No disease
AB (IH and SH)	O	Short + long cubation
AB	A	Long incubatio
AB	B	Short incubati
AB	AB	No disease

O indicates that there is no immunity to he titis viruses A (IH) or B (SH).

(Adapted from MacCallum, F.O.: Hepat Brit. M. Bull. 9:221, 1953) seems probable that the immune state ood recipients is of considerable im- nce in governing the sequence of events wing injection of blood or plasma that contain either or both "Virus IH" (A) Virus SH" (B). MacCallum[45] recently mphasized this as essential to an under- ding of otherwise apparently conflicting rts on the results of studies of hepatitis uman volunteers. Results that might be rved from infection with the two hepati- iruses in accordance with the variation in state of immunity of the recipient are marized in Table 24. The possibility of ltaneous infection of the same person both hepatitis viruses from a single d specimen, resulting in two separate at- s of jaundice within a 6-month period, oteworthy as the second attack in such a ence of events ordinarily might be re- led as a relapse of the initial infection.

CLINICAL AND LABORATORY MANIFESTATIONS OF ACUTE VIRAL HEPATITIS

he variability of the clinical course of viral hepatitis, some of the forms of which were well illustrated by Bloomfield[8] (Fig. 123) in 1938, has not been emphasized sufficiently. The lack of a specific diagnostic test and unfamiliarity with these different clinical variants prevent recognition of many infections that deviate from the familiar typical pattern of acute hepatitis with jaundice. This is particularly true of the nonicteric forms. The following clinical description will refer only to uncomplicated, nonfatal, acute viral hepatitis, and the variants will be described subsequently under "Complications."

Acute Nonicteric Viral Hepatitis

Incidence. Although the incidence of nonicteric infections varies with the particular strain of virus and the age group involved, it is believed that nonicteric hepatitis occurs more frequently than hepatitis with jaundice.

Symptoms. The symptoms of the nonicteric disease are qualitatively similar to those of the icteric form but usually are somewhat less in degree and duration.[29, 56, 59] In young children the symptoms may be predomi-

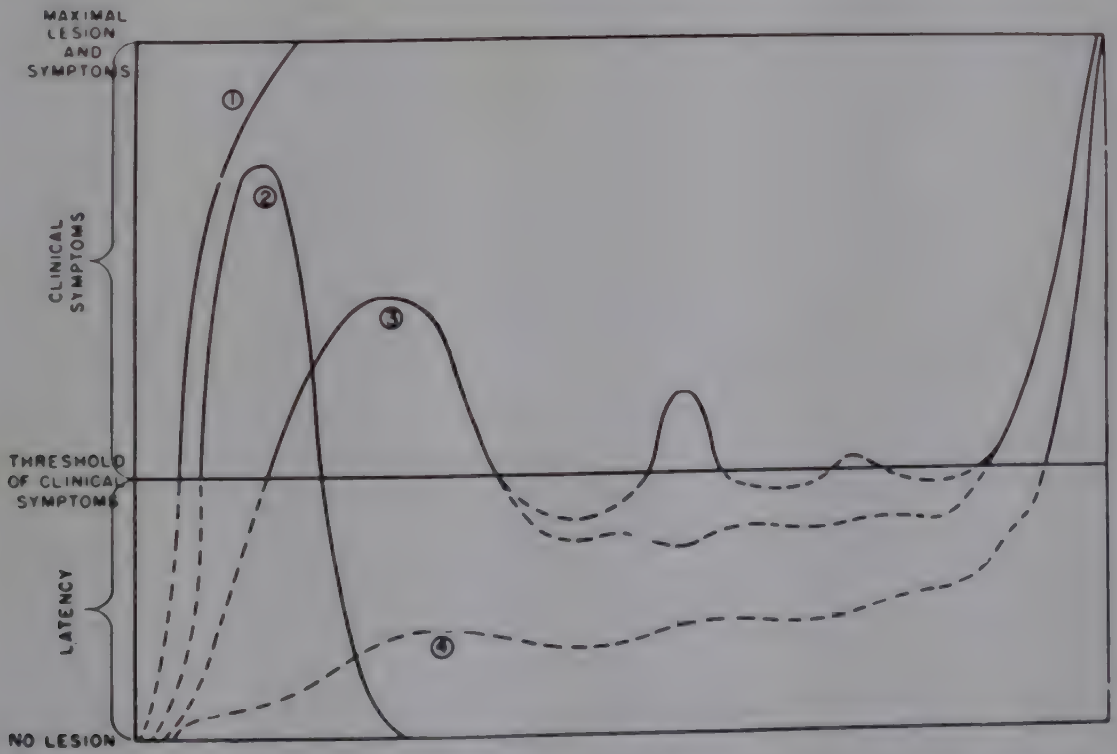

FIG. 123. Variations in the course of hepatitis. (1) Acute hepatitis progressing rapidly to death. (2) Acute hepatitis with recovery. (3) Acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis. (4) Hepatitis latent from the start until advanced liver insufficiency supervenes. (Bloomfield, A. L.: Am. J. M. Sc. 195:429)

nantly those of a gastroenteritis or a diarrheal disease.[10, 11]

Physical Findings. The physical findings may be entirely similar to those of icteric hepatitis except for the absence of overt jaundice. In some, physical findings may be absent. Apparently, at times, the nonicteric disease may pursue a prolonged chronic course. In some such infections, the virus may be present in the blood or the stool for long periods, often without the association of noteworthy symptoms.[84] This nonicteric carrier state undoubtedly represents a dangerous and usually unrecognized source of infection of others.

Laboratory Tests. The results of laboratory tests in nonicteric hepatitis may be entirely similar to those subsequently described for the icteric disease except that hyperbilirubinemia is slight or absent. Urine bilirubin occasionally may be detected even in the absence of hyperbilirubinemia. Particularly in the newborn and very young children, the results of hepatic tests may be quite variable and often may deviate little from the normal. Lacking a specific diagnostic test and with inconsistent responses of the hepatic tests, it is evident that such infections frequently will not be diagnosed and, except when observed during the course of an epidemic, may not even be suspected. Due to the uncertainty of the diagnosis, more precise description of the variants of the nonicteric infections must await the development of a specific diagnostic test.

ACUTE ICTERIC VIRAL HEPATITIS

This is the commonly recognized form of the disease and consists of 3 stages: preicteric, icteric and posticteric. Although *inconstant* differences exist during the preicteric stage, the clinical manifestations of "Virus IH" (A) and "Virus SH" (B) infections during the icteric and the posticteric stages are indistinguishable, and thus the clinical courses of the two infections may be considered as one.

Preicteric Stage. SYMPTOMS. "Virus IH" (A) and "SH" (B) infections differ clinically only during the preicteric stage.[29, 54] Even in this stage there is so much overlapping that reliable distinction between the two types of infection cannot be made on the basis of clinical phenomena alone. *Typical "Viru IH"* infections, as observed under experimental conditions in human volunteers, usually are characterized by a relatively sudden onset. Fever, occasionally a chill, and obvious acute illness are the rule. The acute symptoms are nonspecific and resemble those of a variety of acute infectious diseases or of various acute abdominal syndromes. In contrast, *typical "Virus SH"* infections, a observed under experimental conditions in human volunteers, usually are associated with a comparatively benign, insidious, relatively afebrile onset. The patient often may not be aware of being ill until jaundice appears. All variations of the preicteric stage occur with both infections, and the diagnosi during this period frequently is difficult and often erroneous. Abdominal pain and tenderness may be absent or may be so severe as t suggest an acute surgical emergency. Likewise, the phenomena of acute infectious disease may be entirely absent or may resembl those of severe, overwhelming infection, including prostration, high fever, profoun weakness, generalized myalgia and arthra gia, severe headache, pain in or about th eyes, especially on movement, and a variet of transient cutaneous eruptions. *Weaknes easy fatigue, a sense of depression and a orexia are outstanding*. Nausea usually is intermittently present and occasionally vomi ing. Mild transient diarrhea occurs in som epidemics, but severe prolonged diarrhe due to hepatitis alone is unusual. In occasional epidemics, symptoms of upper-respiratory-tract infection may be noted, althoug this is not the usual case. Temperature us ally returns to normal spontaneously after to 10 days, often with the appearance jaundice. Continued significant elevation temperature for more than a week after th appearance of jaundice is unusual and shou lead to a search for other specific causes jaundice or some associated condition. The may be an abrupt disappearance of all sym toms from 2 to 4 days after the onset whi may lead to release or discharge of the p tient only to be followed by a recurrence symptoms, dark urine and jaundice a f days later.

PHYSICAL FINDINGS suggesting invol ment of the liver may be entirely absent d

he preicteric stage, although some ten-
ess to palpation or fist percussion over
liver may be elicited. Occasionally, en-
ement of the posterior cervical lymph
es may be detected, but generalized
phadenopathy is unusual, although it
occur. Various types of skin eruption,
h as urticaria and patchy or diffuse ery-
na, may be noted. Occasional patients
present the physical findings of the acute
gical abdomen, including muscular rigid-
and marked tenderness to palpation. Such
ings are usually in the epigastrium, RUQ,
occasionally in the RLQ.

The first suggestion of the nature of the
ess during the preicteric stage may be the
pearance of *dark urine* from one to many
s prior to the appearance of visible jaun-
e. One of the most useful *early diagnostic*
oratory aids is the demonstration of bili-
in in the urine, often one to several days
ore a measurable increase in the serum
irubin concentration is present.[55] Excess
ne urobilinogen often provides an early
e, but absence of this finding is of no
nificance. Traces of albumin occasionally
present in the urine during this phase,
rticularly in patients with high fever; but
her urinary abnormalities, as measured by
utine urinalysis, are absent or minimal.
hemia is absent unless another associated
sease exists. The total leukocyte count
rely exceeds 10,000 or 11,000 and ordi-
rily is normal or low. The differential
unt either is normal or reveals an increase
lymphocytes. The frequent presence of
typical lymphocytes," indistinguishable
om those observed in infectious mononu-
eosis, may confuse the diagnosis.[29, 54]
osinophilia is not common but has been
bserved (up to 20% in one case studied
y the author). With *"Virus IH"* infections,
l hepatic tests may be entirely negative
ntil several days before the appearance of
vert jaundice. Urine bilirubin and urobilino-
en and bromsulfalein retention usually are
he first tests to suggest hepatic involvement
uring this period. As some increase in
romsulfalein retention occurs in a number
f febrile states, the urinary abnormalities
re somewhat more specific in suggesting the
iliary tract as a site of involvement. The
ephalin flocculation and thymol tests usually become positive toward the end of the preicteric period or in the early icteric period. However, one or both of these tests may remain negative throughout the entire course of the disease in approximately 20 per cent of cases. With *"Virus SH"* infections, the tests mentioned often are abnormal by the time of appearance of the first symptoms. In fact, test abnormalities frequently appeared *prior to* the development of any symptoms or signs in volunteers with "Virus SH" infections in contrast with those with "Virus IH" infections in which the patient often had severe symptoms and signs for several days before any hepatic test abnormalities were demonstrated.

Icteric Stage. SYMPTOMS. This stage begins with visible jaundice, which usually appears first in the sclerae. It consists of ascending and descending phases, corresponding to the periods of increasing and decreasing jaundice, respectively. The peak of the jaundice is usually reached in 5 to 15 days. During the ascending phase, anorexia, fatigue and occasionally nausea may persist. Often, however, most of the subjective symptoms, including fever, if previously present, subside with the onset of jaundice, and the patient may be quite comfortable throughout the icteric stage. Annoying pruritus occurs in some cases, and this actually may begin during the preicteric stage. Jaundice usually begins to decrease rapidly within a few days after reaching the peak level, the rate of decline decreasing as the serum bilirubin concentration approaches the normal range. A definite diuresis often heralds the onset of the descending icteric phase and is a favorable prognostic sign. Overt jaundice usually disappears after 2 to 4 weeks but, in occasional patients, jaundice may persist at the peak level for weeks before the onset of the descending phase. As indicated by Figure 123, all variations of the above course may occur. Somnolence, irritability, mental depression, and other symptoms referable to the central nervous system may occur.

PHYSICAL FINDINGS during the *icteric* stage include jaundice of any degree, enlargement and/or tenderness of the liver (both may be absent), and occasionally a palpable spleen. If pruritus has been prominent, a scratch dermatitis may be present.

LABORATORY MANIFESTATIONS during the *icteric* stage are of importance in differential diagnosis. The blood count usually is normal, although leukopenia and a tendency to lymphocytosis, as described under the preicteric stage, may persist. Urine examination usually is normal except for the presence of bilirubin. Urine urobilinogen may be normal or increased. The total and 1-minute serum bilirubin both are elevated, the latter constituting approximately 40 to 70 per cent of the total bilirubin. Either or both the cephalin flocculation and the thymol tests are positive with, or very shortly after, the appearance of jaundice in 80 per cent of the patients, although it is emphasized that both may be negative throughout the course of the disease in approximately 20 per cent of the infections. Colloidal gold, colloidal red and zinc turbidity reactions tend to parallel the results of the thymol test and add additional information only in occasional instances.[60] Alkaline phosphatase usually is normal, but moderate elevations may be observed. Occasionally, alkaline phosphatase elevations of the magnitude observed in extrahepatic obstruction may occur. During the early phase of the icteric stage, albumin, and total globulin fractions of the serum are normal unless associated disease is present. If the disease is prolonged and severe, some depression of serum albumin and elevation of serum globulin may occur. Total cholesterol usually is normal or slightly low and the esterified fraction usually is depressed. In those cases with very high alkaline phosphatase, elevation of cholesterol also may be observed. Elevated total cholesterol commonly occurs during the latter part of the descending icteric and posticteric stages.

Posticteric Stage. From the clinical viewpoint, this stage begins with the disappearance of visible or overt jaundice. By this time, all symptoms ordinarily have disappeared while the patient is at rest. Malaise, easy fatigue with mild exertion, and occasionally RUQ discomfort may persist for several weeks. In occasional patients, these symptoms may continue for months.

PHYSICAL EXAMINATION during this stage may reveal no abnormality. Often the liver, if previously enlarged, may continue to be palpable for a variable period. Usually, however, there is a progressive decrease in th hepatic enlargement to the prehepatitis sta within 2 to 6 weeks after the disappearanc of jaundice. Hepatic tenderness normally ha disappeared and, if persistent, suggests continued activity.

LABORATORY FINDINGS. From the laboratory standpoint, the total and 1-minut serum bilirubin may remain elevated at subclinical levels for 1 to 3 weeks after th disappearance of visible jaundice. The tota bilirubin may return to within the norma range before the 1-minute bilirubin does so Bromsulphalein retention usually is increase for a variable period after the disappearanc of overt jaundice, although in some cases th serum bilirubin and bromsulphalein test ma return to normal at approximately the sam time. The sedimentation rate often is markedly elevated during the active disease an this may persist into the posticteric stage It usually returns to normal somewhat before all the hepatic tests are normal. If th cephalin and the thymol tests were positive they tend to return toward the normal rang progressively, the thymol turbidity and th flocculation tests usually being the last t return to normal. In some patients, the flocculation tests, particularly the thymol tes continue to be positive for months afte clinical symptoms have subsided and a other tests are normal. Although some investigators interpret this as a possible immune response, probably without clinica significance, the author is inclined to interpret this phenomenon as evidence of incomplete recovery until proved otherwise This is based on the observation that a these tests become negative in most patient within a month after the disappearance o jaundice.

COMPLICATIONS OF ACUTE VIRAL HEPATITIS

Complete clinical and laboratory reco ery from acute viral hepatitis usually occu within 4 months. The ultimate outlook f the average infection is excellent althoug as compared with most other infection hepatitis is a disease of relatively long dur tion and thus of high morbidity. An unce number of patients may have one of al variations from the usual course of lisease. Most of the available informa- pertains to those patients who have had viral hepatitis *with* jaundice as the nosis frequently is not made in the non- c infections. Likewise, most follow-up mation has been derived from follow-up es carried out on relatively young, male ts.[38, 39, 42, 44, 63, 70, 73, 77, 80, 81, 91] How- , the incidence of complications may with the virus concerned and the age, sex and the over-all condition of the ent. For example, hepatitis acquired n blood transfusion in civilian life com- ly occurs in the older age groups, and patient concerned often has some other ous associated condition which required od transfusion. For these reasons, the uency of complications might be ex- ted to vary under these different circum- ces.

he following important complications are gnized: (1) fatal hepatitis, (2) relaps- and/or recurrent viral hepatitis, (3) pro- ged hepatitis, (4) chronic hepatitis, (5) carrier state, (6) other posthepatitis es—(A) posthepatitis syndrome, (B) erbilirubinemia.

Fatal Viral Hepatitis

Mortality Rates. Reported mortality rates large outbreaks of naturally occurring irus IH" hepatitis usually range in the ghborhood of 0.2 per cent.[29, 41, 56] This ne rate was observed in the remarkable ssive outbreak of "Virus SH" hepatitis t followed inoculation of U.S. troops th yellow fever vaccine in 1942.[65, 75] As ny unrecognized nonicteric cases proba- were not included in the computation, actual rate for this outbreak probably s lower. In other small localized out- eaks, mortality rates following blood or asma transfusions have ranged as high as per cent.[59] A particularly malignant form hepatitis with mortality rates varying from to 50 per cent, affecting mainly elderly omen, has been observed in the Scandina- an countries but has not been proved to be viral origin.[3] It is believed that the varia- ons in mortality rate may be influenced by one or more of the following factors: (1) the particular strain of virus concerned, including the conditions under which it has existed prior to patient entry; (2) possibly the size of the infecting dose; (3) the age, the general health and the immunologic state of the patient (including the presence or the absence of pre-existing liver disease or other associated diseases); (4) possibly the management of the patient, particularly during the acute stage of the disease. The above mortality rates, although quite low in most epidemics and other outbreaks, nevertheless result in a disturbingly large number of fatal cases because of the high total incidence of the disease. Furthermore, these rates do not include the small group of patients dying from advanced liver disease some years after an attack of presumed acute viral hepatitis.

Clinical Picture. From the clinical point of view, the potentially fatal nature of the disease presents a special problem because the initial course of fatal viral hepatitis does not differ from that of the ordinary mild or average infection. Patients with the mildest initial symptoms may suddenly develop rapidly progressive hepatic failure terminating in death within 2 to 5 days.

Death in fatal hepatitis may occur at any stage of the disease, but most of the fatal infections fall within two main types, namely, the fulminant and the subacute types.[43, 50] In the *fulminant form,* death usually occurs within 10 days of the recognized onset, sometimes before the disease has been present sufficiently long for jaundice to become apparent. In the *subacute form,* death usually occurs from 3 to 8 weeks after the onset.[41, 44] In these cases, jaundice often has been prolonged or has been of the relapsing type. Initially, the icteric phase of the disease may have followed the customary pattern with no phenomena suggesting the eventual fatal nature of the disease. In others, there is a slow gradual increase in the degree of hepatic insufficiency. Eventually, a sudden change occurs, often indicated by symptoms referable to the central nervous system, including personality changes, stupor, delirium, or occasionally convulsions. Fever and leukocytosis commonly occur in association with the change in symptoms which also include persistent vomiting, the development of ascites, edema, hemorrhagic phenomena and eventually coma. Coma may develop suddenly or may follow gradually increasing stupor. Occasionally, symptoms due to hypoglycemia, hypocalcemia or electrolyte disturbances may confuse the picture. These factors are important in therapy.

Physical Findings. The physical findings of this stage, as well as many of the symptoms, are variable and similar to those of the terminal stage of hepatic insufficiency from other causes. However, it is generally agreed that the chances of recovery from hepatic coma due to viral hepatitis are less than those associated with hepatic coma resulting from portal cirrhosis, particularly as it occurs in alcoholics.

Laboratory Findings. The laboratory findings are similar to those of advanced hepatic insufficiency from other causes. The degree of jaundice is quite variable, and death may occur even though jaundice is relatively minimal. In other cases jaundice is extreme. Although the leukocyte count usually is normal throughout the course of nonfatal hepatitis, the onset of the terminal stage often is associated with a marked leukocytosis. Hypoglycemia of severe degree is apt to occur and may appear abruptly. Azotemia and severe electrolyte disturbance may be observed; these depend to some extent on treatment (cortisone, ACTH) and the state of renal function which may be well maintained until the end or may fail early in the terminal stage.

As will be mentioned in the next section, a few patients may survive for one to many years with chronic latent or active hepatitis until gradually increasing hepatic insufficiency or other complications of chronic liver disease, such as portal hypertension, lead to death.

RECURRENT AND/OR RELAPSING HEPATITIS

The literature is confusing in respect to the incidence of recurrence or relapse of acute viral hepatitis, particularly when this occurs after an interval of apparent recovery following the initial acute episode. Exacerbations of liver disturbance occurring before clinical and/or laboratory recovery from the initial attack probably are true relapses and apparently occur in 15 to 25 per cent of patients, even when under close supervision and management.[5, 6, 39, 59, 73] Such relapses may be a duplication of the original attack or actually may be more severe. More often, however, relapses are evidenced only by mild aggravation of the degree of hepatic disturbance revealed by hepatic tests. Relapses occur most often at the time when the patient is allowed to return to physical activity. The duration of the relapse may be short or may extend beyond the period of the initial acute episode. Although relapse prolongs the duration of the disease, most patients ultimately achieve a complete recovery within 1 year. Available data suggest that only approximately 5 per cent of patients that have relapses fail to achieve an apparent recovery within that period.

When another episode of acute liver disease occurs following apparent recovery from an initial attack of acute viral hepatitis, the relationship of the second episode to the first becomes less certain with the passage of time.[63] Thus, most *true* relapses probably occur within 6 months of the initial attack, and the clinician must be alert to the possibility of some other cause of the second episode at all times. Thus, in persons with two separate attacks of jaundice separated by several months, there is the additional possibility that the first episode represented an "IH" infection and the second an "SH" infection. It is theoretically possible that both of these viruses might be transmitted to the same person by the same blood transfusion or blood product. When the patient is first seen during the second attack, there always is a question of the diagnosis during the first attack. Thus, one occasionally finds that the diagnosis was erroneous for the first attack and that one is dealing with multiple attacks of jaundice due to extrahepatic biliary obstruction. The author has observed a patient with known acute "Virus IH" hepatitis who, 6 months later, developed a second attack of jaundice proved to be due to infectious mononucleosis. It seems likely that second episodes, representing an exacerbation of the initial disease, usually will occur during the early months after the subsidence of the first acute episode. One should be very cautious about attributing second attacks of jaundice occurring after 6 to 12 asympto-

c months to an exacerbation of the origi-
nfection. On the other hand, apparent
very following an initial attack cannot
udged safely on the basis of clinical ob-
ation alone. Thus, complete recovery
ld be based on clinical judgment sup-
ed by proof of laboratory recovery as
. Unfortunately, most patients with acute
titis observed in civilian practice are
harged as recovered on the basis of the
idence of the jaundice and the clinical
ptoms without adequate laboratory
w-up.

PROLONGED HEPATITIS

his term is used herein for those infec-
s in which clinical and/or laboratory
ence of active hepatic disease persists
tinuously for more than 4 months, but
n which apparent complete recovery ul-
tely occurs, usually within 18 months.
h infections have been referred to by
ers as "chronic hepatitis."[6] It seems pref-
ble to the author, however, to distinguish
e patients who ultimately recover com-
ely after a prolonged course from those
do not. A number of the infections in-
led under the group designated as "re-
ing hepatitis" also could be classified as
olonged hepatitis." However, again it
ms desirable to separate those infections
hich the disease is continuous from those
which the course is marked by one or
re distinct attacks of uncertain relation-
and between which there is an apparent
overy. The available data, which refer
inly to acute hepatitis with jaundice in
lt males of military age, suggest that from
to 20 per cent of the acute icteric infec-
s will fall into the category of "prolonged
atitis" as defined above. However, the
idence of prolonged hepatitis may be
her in other groups, possibly varying with
same factors that influence mortality (see
tal Hepatitis").

n 3 groups of patients with prolonged
atitis for which adequate follow-up data
available, only approximately 5 per cent
ed to achieve an apparent complete clini-
and laboratory recovery by the end of 1
r.[6, 38, 39, 56, 59] During this interval, the
nd was usually one of slow gradual im-
vement at varying rates, the manifestations obviously varying with the time of observation. The findings in general were those associated either with a prolongation of the icteric and/or the posticteric stages of the acute disease. Among those exhibiting a prolonged icteric phase, a few present certain features that differ from the usual course in their laboratory and, to a lesser degree, in their clinical manifestations. In these patients, moderate to severe jaundice may persist for months in spite of relative well-being of the patient. Pruritus and easy fatigue with ordinary exertion may be the dominant symptoms except for the jaundice. The hepatic tests often are identical with those of posthepatic obstructive jaundice, namely, negative or variable flocculation tests in association with moderate to marked elevations of alkaline phosphatase and serum cholesterol. Differentiation of these infections from the surgical types of jaundice often is extremely difficult on the basis of clinical or laboratory evidence, and at times, needle biopsy of the liver may fail to make a reliable distinction. The term *cholangiolitic hepatitis* has been applied to this syndrome.[1, 87, 88] As histologic evidence of cholangiolar disease is not recognized in these cases, some have objected to this term. In fact, many pathologists state that they are unable to recognize any difference between this form of hepatitis and the usual clinical form on histologic grounds alone. Nevertheless, there is no doubt that this form of the disease exists as a clinical and laboratory entity in which the phenomena are primarily those of extrahepatic or intrahepatic obstruction. It has been suggested, however, that the process may cause a disturbance in excretion and absorption across the biliary epithelial membranes rather than intrahepatic obstruction. Although patients with this form of the disease recover completely after a prolonged icteric course, the process in others develops into the chronic hepatic disease which has been referred to as *cholangiolitic cirrhosis*.[87, 88] Although the clinical and laboratory phenomena tend to follow the course of either the usual or the cholangiolitic forms from the onset of the disease, the phenomena of the latter occasionally may develop during the icteric stage of the former.

Chronic Viral Hepatitis

This term will be used herein for the remaining small group of patients in whom clinical and/or laboratory evidences of liver disease persist continuously for more than 1 year after the initial onset of viral hepatitis. The degree of hepatic disturbance may vary but persists continuously, in clinical or subclinical form, with or without jaundice. It is believed that some such infections, with active disease persisting for several or more years, eventually may resolve in a clinical and hepatic functional recovery. However, inadequate clinical or hepatic histologic studies of a group of such patients are available to determine if these patients actually have a healed or only a temporarily quiescent disease. More often, the patients of this group gradually suffer a progressive liver injury, with increasing hepatic insufficiency, which eventually leads to death from the latter or one of the complications of chronic liver disease. The frequency with which the chronic form develops, as herein defined, can be approximated only roughly. Again, the available data refer only to follow-up studies of young men of military age and do not include nonicteric cases. Thus, the actual incidence may be quite different with particularly virulent strains and in hosts of different age groups with different associated conditions and states of general health. Based on the available data, it would appear that approximately 4 per cent of those who suffer from "prolonged hepatitis" may develop the chronic disease as defined above. This would represent an approximate incidence of only 0.6 per cent of the acute infections originally associated with jaundice. The author has been impressed with the number of persons with advanced chronic disease of the liver, representing some form of chronic hepatitis, who do not have a preceding history of a typical acute attack with jaundice but have been known to have a prolonged period of a nonicteric hepatic disease, which resembles that observed in *prolonged nonicteric hepatitis*. In fact, in his own practice, this type of chronic disease is encountered more commonly than chronic hepatic disease following an acute attack initially associated with jaundice. Until the etiology of this chronic liver disease preceded by a long nonicteric phase, withou an original acute icteric attack, is clarified it is difficult to be certain whether the low incidence of chronic hepatitis following recognized attacks with jaundice may not misrepresent the true incidence of chronic disease resulting from viral hepatitis.

Clinical and Laboratory Phenomena. The clinical and laboratory phenomena of chronic hepatitis are similar to those of other chronic liver diseases and cirrhosis.

Physical findings may include spider nevi, palmar erythema, ascites and edema gynecomastia, hepatomegaly with or without splenomegaly, splenomegaly with or without hepatomegaly, with or without jaundice. Evidences of portal hypertension may or may not be present. The phenomena of hypersplenism may be observed occasionally

The type of morphologic change in the liver apparently is variable.[1, 8, 36, 38, 49, 50, 68 70, 77, 80, 88, 91] Death usually occurs either from profound hepatic insufficiency or from one of the complications of portal hypertension. The liver at postmortem apparently most often presents the change described as postnecrotic cirrhosis. In others, the picture has been described as multiple nodular hyperplasia or as that of portal cirrhosis. Those patients who have had the so-called "cholangiolitic" form of the disease may present the picture of primary biliary cirrhosis. A these forms of chronic liver disease all are described elsewhere in this text, no furthe consideration is warranted herein.

Although the occasional transition of vira hepatitis into one or the other above-mentioned forms of cirrhosis seems to be wel substantiated, the infrequency of this occurrence deserves emphasis. In fact, recen comprehensive follow-up studies of veteran living in different sections of the Unite States after discharge from military servic made from 4 to 8 years after a previous a tack of acute viral hepatitis with jaundic indicates that the incidence of chron hepatic disease is no greater in this grou than in a group of controls without histo of acute hepatitis with jaundice.[63, 91] Durin their extensive studies of postmortem mat rial during World War II, Lucké and Ma lory[41, 49, 50] likewise were unable to establi any consistent association between cirrho previous hepatitis. However, most of studies were concerned with fulminant ubacute fatal hepatitis. In other words, ugh cirrhosis apparently may follow an k of hepatitis, the available data suggest cirrhosis is no more frequent in persons have had hepatitis 4 to 8 years previ- than in those who have not had recog- hepatitis. All of the above studies are ect to certain limitations which prevent acceptance as conclusive evidence of ack of a strong relationship between cir- is and antecedent hepatitis. In the first e, these studies were limited in respect to and sex, dealing largely with males of ary age. Second, they were concerned ost exclusively with the end results of e hepatitis with jaundice. As mentioned er, many patients encountered in clini- practice with advanced liver disease, that t now be classified as chronic hepatitis cirrhosis of unknown etiology, have had nicteric disease of long duration before cal manifestations or medical examina- leads to demonstration of the presence his disease. It is entirely possible that icteric hepatitis may be responsible for nic hepatic disease with cirrhosis more uently than acute icteric viral hepatitis. is, the exact relationship between an te viral hepatitis, icteric or nonicteric, st await the results of further study after ecific diagnostic test becomes available. haps supporting the possible greater sig- cance of nonicteric hepatitis, as an etio- c factor of importance in development of atic cirrhosis, is the recent demonstration several asymptomatic persons, with no ecedent history of hepatitis or jaundice, h evidence of hepatic cirrhosis who also e been shown to be long-term blood car- s of hepatitis virus.[64] In these persons, er factors, such as alcoholism, may have tributed to the hepatic cirrhosis, but the sence of hepatitis virus in the blood eam over long periods would appear to be re than coincidental.

THE CARRIER STATE

During the last several years, conclusive idence has been obtained that long-term od and fecal carriers of hepatitis virus ist.[64, 84] The majority of the proved carriers have had no history of previous acute hepatitis with jaundice. Likewise, the majority have had no specific symptoms or conclusive physical findings. Although most of the proved carriers have had some evidence of hepatic disturbance demonstrable by hepatic tests, and several have had evidence of advanced liver disease demonstrated by liver biopsy, others have been entirely free of symptoms and of hepatic abnormalities as demonstrated by laboratory tests. In this last group, unfortunately, liver biopsies have not been available. One such carrier was a young mother whose newborn infant developed hepatitis, suggesting the possibility of in-utero transmission. The carrier state of the mother, in this instance, was demonstrated by transmission experiments in human volunteers.[84] Again, further clarification of this state must await development of specific diagnostic tests other than the human volunteer method.

OTHER POSTHEPATITIS STATES

Attention also has been directed to a small group of patients who continue to have subjective complaints of anorexia, fatigue, abdominal discomfort and various nonspecific gastro-intestinal symptoms for prolonged periods after apparent recovery from acute hepatitis.[12, 81] The term "*posthepatitis syndrome*" has been applied to this condition in which other objective evidences of continued hepatic disturbance, including needle biopsy of the liver, cannot be demonstrated. It is believed that the symptoms of these patients are on a psychosomatic basis. Frequently, a reason, such as loss of a pension or other convenience of illness, accounts for the need of continued symptoms in such patients. However, this diagnosis should not be made without proof of normal liver histology, as it has been demonstrated that active hepatic disease may be present in the absence of other laboratory evidence of hepatic disturbance.

Constitutional or Familial Hyperbilirubinemia. Finally, one other condition, considered by some to be the result of viral hepatitis, namely, the syndrome of so-called constitutional or familial hyperbilirubinemia, deserves mention at this point.[16, 89] This condition is characterized by an elevation of the indirectly reacting serum bilirubin, with normal direct-reacting bilirubin and also normal hepatic function as measured by all other available tests, and without evidence of hemolysis or other known mechanisms of hyperbilirubinemia. Liver biopsy in such patients apparently reveals what is considered to be normal morphology. Patients with this syndrome frequently are asymptomatic. Others have occasional periods of vague and nonspecific symptoms, which may vary with fluctuation in the level of the serum bilirubin, but with no other demonstrable evidence of active disease. In a few such patients, functional hypoglycemia is the cause of such symptoms and may be part of the syndrome. Although this syndrome has been observed in patients who have had a definite history of previous acute viral hepatitis with jaundice, frequently it is observed in persons without such history. It seems possible that those who are observed with this syndrome, after viral hepatitis, may have had this condition prior to the attack of viral hepatitis. At the present time a relationship between the two cannot be confirmed or denied, and further clarification again must await the development of specific diagnostic tests.

DIAGNOSIS

As mentioned previously, specific diagnostic tests for viral hepatitis have not been developed. The diagnosis thus depends mainly on clinical and epidemiologic evidence, the pattern of response of certain nonspecific laboratory procedures, and the exclusion of other diseases. The presenting problem usually is the establishment of the condition as one of the types of viral hepatitis or the sequellae. The conditions from which this disease must be differentiated vary according to the stage of the disease. The clinical and laboratory characteristics of viral hepatitis in the various stages have been detailed in the preceding section.

Preicteric Stage

During the *preicteric stage,* or in *nonicteric hepatitis,* the manifestations may simulate those of a variety of acute infectious diseases, those of an acute condition within the abdomen, or those of any one of the gastroenteric disorders. This great variability in the type of onset of viral hepatitis requires constant consideration if errors in diagnosis are to be avoided. For this reason the diagnosis of viral hepatitis usually is not made until jaundice appears, which may be several weeks after the onset of symptoms. During this *early* stage, tenderness or pain in the hepatic area should arouse suspicion. These symptoms frequently are absent, however, as are other local manifestations pointing toward the liver or biliary tract. In such cases, the diagnosis may be suspected by the alert clinician from the application of a group of hepatic studies. The daily inspection of a urine specimen often should suffice. Except for this, the most useful tests at this stage are the bromsulfalein excretion test, the determination of bilirubin and urobilinogen in the urine, measurement of the serum bilirubin (total and prompt direct reacting) concentration, and the flocculation tests. Although positive results with any of these tests will not *establish* the diagnosis of viral hepatitis, they may provide an important clue that, at least, should narrow the field of diagnostic possibilities. In so far as the history is concerned, the absence of a history of contact has no value in excluding the diagnosis of viral hepatitis because of the many potential sources of infection as described in the section on epidemiology.

Icteric Stage

The problem in diagnosis during the icteric stage is essentially that of the differential diagnosis of jaundice. A discussion of this problem is covered in detail elsewhere in this text. It is emphasized that the *age* of the patient affords litle evidence for or against the diagnosis. Viral hepatitis is the most frequent cause of jaundice (other than in the newborn) in children and young adults. The susceptibility of persons in the older age groups to "Virus SH," and their frequent exposure to the mechanisms by which this virus may be acquired from blood, perhaps together with a greater distribution of the hepatitis viruses among the general population, have resulted in the frequent occurrence of viral hepatitis in these older age groups. This creates a particular diagnostic problem with "Virus SH" hepatitis, the onset of which often is that of a relatively insidious, progressively developing jaundice. This mimics the textbook picture of posthepatic obstruction of the biliary tract. Thus the diagnosis of viral hepatitis must be considered seriously regardless of age. Its recognition is particularly important, since patients with viral hepatitis often tolerate surgery poorly, the risk associated with surgery being considerably greater (although less today than in the past) than that associated with operations for jaundice of posthepatic obstructive origin. It is likewise desirable to avoid undue delay in the exploration of patients with posthepatic obstructive (nonreceding) jaundice. However, if bacterial cholangitis is absent, such patients rarely suffer from a period of "watchful waiting," often an important aid in the diagnosis.

The differential diagnosis, therefore, of "surgical" and "medical" jaundice is of importance, and viral hepatitis, at times, offers considerable difficulty in this respect. The presence of strongly positive cephalin-cholesterol and thymol tests during the early weeks of jaundice affords evidence in favor of an intrahepatic cause of jaundice. If the jaundice is severe, a normal, or only slightly elevated, alkaline phosphatase activity is more consistent with an intrahepatic than with a posthepatic obstructive cause. Under the same circumstances, normal total serum cholesterol, with a marked decrease in the quantity of esterified cholesterol, is more consistent with an intrahepatic than a posthepatic obstructive cause. Unfortunately, an important element of intrahepatic obstruction (or disturbance of the biliary epithelial absorption-regurgitation mechanism) frequently occurs during the course of hepatitis and other types of intrahepatic disease. In such cases, the presence of an increased alkaline phosphatase activity and a high total cholesterol concentration may suggest, falsely, the presence of a posthepatic obstruction. Also, one or more of the flocculation tests may be negative, further complicating the picture. In these instances, needle biopsy of the liver may or may not be of value in determining whether the cause of the jaundice is intrahepatic or posthepatic in origin. Although the jaundice eventually may be proved to be of hepatic origin, it must be admitted that the diagnosis of viral hepatitis often remains presumptive and that many such cases actually may be of toxic or other origin.

POSTICTERIC STAGE

During the posticteric stage, the persistence of vague symptoms, including weakness, malaise and vague gastro-intestinal complaints, may be responsible for sufficient disability to require special study and management. In some persons, these symptoms may be the result of other conditions that existed prior to, or developed during the course of, or following, the attack of acute hepatitis. There is no doubt that in some patients the symptoms may be due to persistence of the hepatitis. Careful and detailed study may be necessary to identify the cause properly. Differentiation is essential, as proper management, in one type of hepatic disturbance, may affect adversely symptoms from another source, for example, those of psychosomatic origin. The greatest assistance in the diagnosis of the role of viral hepatitis in these conditions again comes from the laboratory. The tests of most value for revealing the existence of mild degrees of subclinical hepatic disease are the bromsulfalein excretion test, the test for urinary urobilinogen (preferably the quantitative extraction method applied to a 24-hour specimen), measurement of the total and prompt direct reacting serum bilirubin, and the cephalin-cholesterol flocculation, thymol turbidity and flocculation tests, and the zinc turbidity test. When evidence of hepatic disturbance is obtained, it must be realized that these tests are not specific for *viral* hepatitis. When such symptoms persist for prolonged periods or are detected in patients with a prior history of viral hepatitis, one is not necessarily justified in assuming that the condition results from the viral hepatitis.[63] Other medical conditions associated with hepatic disturbance require exclusion, and often biopsy of the liver is essential. In the author's experience, some other cause of the symptoms, particularly pain, has been found frequently. Much depends, of course, on whether the patient has a motive for "incomplete recovery."

Since recent studies have shown that significant morphologic alterations in the liver may be present in association with minimal or no detectable biochemical evidence of hepatic dysfunction, needle or other biopsy of the liver frequently is essential to the proper clarification of the nature of these conditions. A detailed discussion of liver biopsy is presented elsewhere in this text.

Finally, a relationship of viral hepatitis to certain chronic diseases of the liver has been suggested. At the present time, the nature of this relationship is obscure. In addition to establishing the diagnosis, in order to make certain that chronic jaundice with hepatomegaly and/or splenomegaly is not secondary to undiagnosed lesions of the extrahepatic biliary tract, clarification of the nature of the process is essential to the selection of the proper type of treatment. Needle biopsy of the liver, extensive x-ray and laboratory study, or exploratory laparotomy, may be required to solve the problem.

The development of newer technics in x-ray examination of the biliary tract offers promise of additional assistance with some of these puzzling problems. Preliminary results with a new intravenous contrast medium, *biligrafin,* has indicated that visualization of the extrahepatic biliary passages frequently is possible in many nonicteric and some icteric cases.[35] (See also discussion of roentgen examination in Chap. 7.) Thus the exclusion of obstructive lesions of the posthepatic biliary tract may be possible more often than in the past. When properly trained personnel are available, the technic of direct cholecystography and cholangiography, in conjunction with peritoneoscopic examination, is useful.[32] In spite of the application of all diagnostic measures mentioned, the establishment of an accurate diagnosis may not be possible in certain patients. In these instances, exploratory laparotomy may be necessary if an obstructive lesion of the extrahepatic biliary tract cannot be excluded.

As acute viral hepatitis often can be diagnosed only by exclusion, a knowledge of the responses of other diagnostic procedures in this disease often may be of value. The behavior of the blood count already has been described in connection with the clinical manifestations of the disease. The heterophile antibody test usually is negative b
may reach a titer as high as 1:56, positi
titers in higher dilutions rarely being e
countered.[30] This antibody is completely a
sorbed by boiled guinea-pig kidney and th
can be differentiated from that associat
with infectious mononucleosis. Serolog
tests for other specific infections are n
known to be influenced by acute viral hep
titis. The sedimentation rate may be norm
or elevated and, if elevated, may persist f
a long period after jaundice has disappeare
usually in association with other evidenc
of persistent hepatic disturbance. Sustain
falsely positive serologic tests for syphi
are uncommon, although occasional patier
may develop transient positive reactions
Cold agglutinins usually are absent.

PREVENTION

Prevention of viral hepatitis is particula
difficult because of the lack of methods
recognition of virus carriers, the many
tential methods of transmission, and the
usual resistance of the hepatitis viruses
many procedures that eliminate, inactiv
or destroy most pathogens.

Prevention of the spread of hepatitis
ruses involves the consideration of ev
person as a potential carrier. The pro
sources of hepatitis viruses are feces
blood. *The prevention of the spread of*
fection from feces involves all of the c
mon measures associated with the contro
the common intestinal pathogens. Sugge
measures include the improvement of
eral sanitation of camps, institutions,
living quarters; insect control; sterilizatio
food receptacles; observation, examinat
and regular checking of food handlers
cent studies[64] suggest the advisability o
quiring periodic hepatic tests on
handlers); and prevention of fecal cont
nation of food, water, milk supplies
fomites. Adequate disinfection of drin
water is particularly important, and si
chlorination of grossly contaminated
with high organic content without rega
free chlorine residual is not dependable

Prevention of the spread of hepatiti
ruses in blood has raised many new

As the presence of hepatitis viruses in
lood cannot be demonstrated other than
ansmission experiments in human volun-
and, up to date, no method for inactiva-
of the virus in blood is available, the use
hole blood or plasma for transfusion
inues to be associated with the risk of
hepatitis. The recent demonstration of
ptomatic blood carriers, without history
revious viral hepatitis with jaundice, is of
icular importance in this respect.[64, 84] At
present time, human serum albumin solu-
appears to be free of the risk of viral
atitis, as the stability of this material is
as to enable it to withstand sufficient
ing to destroy the hepatitis virus. Like-
, human immune serum (gamma) glob-
. as prepared by the alcohol precipita-
method, has not been associated with
l hepatitis. Ultraviolet irradiation has *not*
ved to be dependable as a method for
tivation of hepatitis virus in plasma, and
e of the chemical methods of sterilization
blood or plasma proposed to date has
n proved to be satisfactory or depend-
, although several promising agents are
ng explored.[18, 27, 51, 90] Storage of plasma
he liquid state (not dried) at room tem-
ature 6 months or longer may be asso-
ed with a decrease in incidence of the dis-
e.[2] However, this method is not applicable
whole blood and is exceedingly cumber-
ne as a method for the treatment of
sma. Storage at room temperature for 3
nths in the liquid state has been shown to
ineffective for the inactivation of hepatitis
is.[5] At the present time (1954), there-
e, there is no entirely satisfactory method
the elimination of hepatitis virus from
ole blood or its products other than albu-
n and gamma globulin (as now prepared).
r this reason, whole blood, plasma and
blood products, other than albumin and
nma globulin, should not be used unless
indications outweigh the risks of a po-
tial attack of viral hepatitis. The newer
od fractionation products, prepared by
wer methods, are untested. In evaluating
s, it appears that the risk increases pro-
rtionately with the number of units of
sma involved. Thus pooled plasma, or
ltiple single transfusions, will be associ-
ed with a higher risk than with the use of
single blood transfusions. No reliable data are available concerning the incidence of carriers of hepatitis virus. However, existing information suggests that blood carriers among the normal population, in some areas at least, may range between 1 and 5 per cent. This figure might be higher if transient asymptomatic carriers are included. Thus, prevention of transmission by this means can be accomplished best by the avoidance of the use of such blood, or its products, unless necessary. Recent studies have suggested that a high percentage of asymptomatic blood carriers of hepatitis virus may have detectable evidence of hepatic disturbance as indicated by hepatic tests.[21] Approximately 10 per cent of random blood donors exhibit a significant abnormality with one or more of a group of sensitive hepatic tests (total and 1-minute serum bilirubin, bromsulfalein, zinc turbidity, thymol turbidity and flocculation, urine urobilinogen). As the hepatic abnormality in most of the proved infectious asymptomatic donors[64] was reflected by abnormal thymol and zinc turbidity tests, it is probable that a significant number of potentially infectious donors could be excluded if these tests were performed routinely on all blood donors in the same fashion as the routine culture and the serologic test for syphilis. Such methods will not eliminate the problem of blood transmitted hepatitis but possibly may aid in a reduction of the incidence.

Unfortunately, the development of satisfactory methods for inactivation of hepatitis virus in blood and its derivatives will not eliminate all of the problems associated with the transmission of these viruses from blood. The other mechanisms of transmission (Fig. 122) associated with the use of improperly sterilized needles, syringes, lancets and other instruments coming in contact with blood or its products will remain as sources of infection. Elimination of these methods of transmission involves the use of adequately sterilized instruments for each patient. This applies to instruments used for such routine procedures as blood counts and needles and syringes used for simple venipuncture or injections. The minimal procedures necessary to disinfect such instruments adequately have not been determined accurately. Simple rinsing and immersion in alcohol or other disinfectants has not proved to be dependable. This perhaps may be largely a matter of the undependability of technics performed by human beings. Thus adequate exposure to proper chemical disinfectants for a sufficient length of time undoubtedly is capable of disinfecting hepatitis virus. However, the information necessary to establish the minimal requirements is not available. For this reason, adequate sterilization of such instruments requires, at the present time, thorough cleansing of all instruments to ensure removal of all traces of foreign material, such as blood clots, followed either by boiling or autoclaving for 20 minutes.

"Virus SH" has not been infective when administered by the oral route, and the stools from patients with "Virus SH" infections have not been shown to be infectious. Most such studies have involved inoculation by the oral route and, as this virus appears to be infective only by the parenteral route, the absence of this virus in the stools has not yet been proved adequately. Patients known to have this infection ordinarily would not require isolation. Unfortunately, in most sporadic cases of viral hepatitis it is not possible to be absolutely certain whether "Virus IH" or "Virus SH" is concerned. Therefore, it is necessary to assume that both the stool and the blood are infectious in the management of most patients with this disease. Although the virus apparently does not spread easily or rapidly through hospital wards, this and spread through a family do occur occasionally. The high morbidity and occasional mortality thus require that precautions against infection be instituted in the management of such patients whenever feasible. In most families, other members of the family usually have had maximal exposure by the time that the diagnosis is made, and institution of strict precautions then probably is useless. All those in contact with the patient should be instructed to wash their hands thoroughly with soap, preferably followed by a disinfectant, after handling any article that may have come in contact with the patient. Hospitalized patients should be placed under precautions that are similar to those instituted for other infectious enteric diseases plus the general measures taken to avoid transmission from blood. In this respect, particular care should be exerted in the handling of patients with colostomies or ope lesions associated with the oozing of bloo or serum. As many of the patients with vir hepatitis are surgical patients, contact wit such materials is common among those involved with dressing of wounds.

"Virus IH" infections can be prevente by the intramuscular injection of normal human serum globulin in a dosage of 0.02 c per kg. of body weight if administered pri to the onset of symptoms and signs of th active disease.[28, 82, 83] If such gamma globulin is available, it should be given routine to all those exposed in the course of a spreading epidemic, to those exposed heavily individual cases, and to those accidental receiving unusual exposure by other mech nisms. Although such gamma globulin a parently does not protect against "Virus SH infections,[7] one often is not certain about t type of infection concerned in individual p tients. Supplies permitting, prophylactic i jections of gamma globulin would be d sirable in all patients receiving multip blood transfusions.

There is some evidence to suggest th those injected with gamma globulin, w continue to be exposed and are infected hepatitis virus during the period of passi production, may actually benefit from a s called "active-passive" immunization resu ing in prolonged immunity.[84]

TREATMENT

Although no specific treatment for vi hepatitis is available, the natural tendency the disease is toward spontaneous recove Thus, most patients will recover fully a completely with no treatment other than striction of physical activity during the ac stages of the disease and a high-caloric, hi protein, high-carbohydrate, moderate diet. Unfortunately, the disease is unp dictable, and it is not possible to determ at the onset which infection may be fata may be followed by one of the other vari from the usual course of prompt and sp taneous recovery. Thus, it is necessary treat all patients with hepatitis initially a potentially fatal or serious disease d otherwise. Because of the great varia- of the course of the disease, it is im- ble to outline a standard treatment am. The basic principles of treatment restriction of physical activity and , 6, 62 The concepts concerning the de- of restriction of physical activity and omposition of the diet are undergoing change as the result of recent studies . S. Army troops in Korea.[13, 40] Based hese studies, a Committee on Hepatitis e Commission on Liver Disease of the ed Forces Epidemiological Board[13] has d the following statement regarding the ment of *uncomplicated* acute viral titis:

> ne following recommendations for the ment of acute infectious hepatitis are gen- principles and may require modification he individual patients under particular cir- stances. They embody a distinct change in presently accepted rest regimen and little o change in dietary treatment. They are d on the conclusions of a carefully con- ed study of enlisted military personnel acute infectious hepatitis. Their applica- y to the more severe forms of the disease lder or less well-nourished patients has not established.
>
> nce physical activity to the point of fatigue be harmful, patients with acute hepatitis ld be hospitalized as soon as the diagnosis ade. They should be urged to rest in bed ong as acute symptoms persist. Once they n to feel well, regardless of the degree of dice, they should not be forced to stay in more than an hour after each meal. Re- tion to the hospital ward, however, is ntial to decrease undue activity or exertion. wing ad lib activity on the ward (without required exertion) circumvents the usual y necessary for recuperation from the cts of prolonged rest in bed and appreci- y shortens the periods of hospitalization.
>
> atients so treated may be discharged from hospital, and physical reconditioning may undertaken after the total serum bilirubin elow 1.5 mg. per 100 ml. and the brom- falein retention in 45 minutes below 6 per t for a period of not less than one week. tients whose bromsulfalein retention stabi- es between 5 and 10 per cent may be dis- rged from the hospital with safety. Those h persistently higher levels will require in- idual management.
>
> Following discharge from the hospital it is well to follow all patients for two weeks with weekly physical examinations, serum bilirubins and bromsulfalein tests. Recurrent abnormalities will occur rarely and are probably indications for rehospitalization.
>
> The optimal diet in the treatment of infectious hepatitis consists of about 3,000 calories containing approximately 150 grams each of protein and fat. Intakes above this level should be ad lib. Although fried and greasy foods may cause indigestion, the fat contained in meat, eggs, and dairy products is not harmful and adds greatly to the palatability of the diet. During the stage of severe anorexia the patient should be urged to take frequent small feedings. Intravenous glucose solutions should be administered when necessary to maintain a minimal caloric and fluid intake. Although the forcing of a high protein, high fat diet, by stomach tube if necessary, has been demonstrated to hasten recovery in the average infection, critically ill patients with fulminating disease or impending hepatic coma may be harmed by excess dietary protein.[71] In these few patients, therefore, it is probably unwise to administer more than a maintenance quantity of protein.
>
> Intravenous protein hydrolysates, plasma or blood transfusions have no place in the nutritional therapy of patients with uncomplicated infectious hepatitis.

Transfer of the above principles of therapy for the management for acute viral hepatitis in military service to the treatment of patients encountered in civilian practice must be modified by discretion. When the disease is acquired by persons of older age groups with other associated diseases, bed rest probably should be maintained until the descending icteric phase is well established and the patient is completely asymptomatic. Also, the resumption of physical activity probably should be carried out more cautiously and with closer follow-up supervision.

The symptoms of acute viral hepatitis are most prominent during the preicteric and the early icteric phases. Anorexia often is severe and may be associated with troublesome nausea. Until this stage is passed, daily intravenous infusions of 10 per cent glucose with vitamin supplementation is desirable. For nausea, the use of Benadryl, pyribenzamine, or Dramamine in doses of 50 mg. before the main meals may be very helpful.

The mild sedative action of Benadryl taken at bedtime may promote rest. The use of Vitamin B_{12} has been considered by some as beneficial. If the nutritional status prior to the onset of hepatitis has been satisfactory and prolonged dietary inadequacy does not occur during the early stage of the disease, there is no definite evidence that the use of the lipotropic agents such as methionine and choline is beneficial. If there is doubt about the prior or present nutritional status of the patient, the author often prescribes methionine in a dosage of 1 to 3 Gm. daily until the patient is capable of taking the recommended diet. Appropriate measures to avoid colon stasis also are advisable. Additional therapeutic aids employed in the treatment of the fulminant overwhelming infections and hepatic coma are described elsewhere in this text.

The treatment of *relapse* should include resumption of those measures employed during the initial active symptomatic phase of the disease, including bed rest. Present available information suggests the possibility that a relapse may prove to be an indication for treatment with cortisone or ACTH. In addition, patients with tendency to relapse should have a thorough medical evaluation to exclude the presence of associated conditions such as other intestinal infections, including amebiasis, or an incorrect original diagnosis. Any such conditions should be treated appropriately unless the indicated treatment is likely to be more hepatotoxic than the condition itself.

In some patients who fail to recover progressively, treatment with one of the broad-spectrum antibiotics, such as chlortetracycline (Aureomycin) in a dosage of 250 to 500 mg. 4 times daily for 2 to 4 weeks may aid in initiating recovery if such therapy is well tolerated otherwise.[79]

A few patients will continue to have weakly positive hepatic tests for prolonged periods in spite of the absence of symptoms and significant physical findings. In such patients, who fail to exhibit progressive improvement on conservative therapy, a cautious trial of increased physical activity, with laboratory follow-up of the effect, may be necessary.

A decision as to when it is safe to resume physical activity following hepatitis often
difficult, since there are no standard obje
tive criteria that may be employed. Und
the treatment program outlined above, f
military personnel, most patients will be am
bulatory by the time the serum bilirub
returns to normal. Before any further in
crease in activity is permitted, the brom
sulfalein retention should be 8 per cent
less at 45 minutes, and the thymol ar
cephalin flocculation tests no more tha
weakly positive. Likewise, the liver shou
no longer be grossly enlarged or tende
Under these circumstances, a very gradu
increase in physical activity, beginning wi
short walks, may be permitted and increase
progressively. The remaining abnormal la
oratory tests should be repeated 1 week aft
such increase in activity. The occurrence
any adverse symptoms, such as persiste
fatigue without exertion or gastro-intestin
symptoms, should lead to prompt re-evalu
tion. Allowance must be made for the
currence of fatigue with increasing exerti
which may be the result only if the pr
longed period of physical inactivity. Wh
the amount of physical activity that or
narily is involved in one's usual occupati
is reached, resumption of work may be p
mitted. It is desirable, particularly for th
who are employed by others and are unal
to control their time, to recommend th
only half-time work be undertaken dur
the first week. If this is well tolerated, f
time work may be resumed. Alcoholic b
erages, prohibited until this time, proba
may be used safely in *minimal* quanti
after all the hepatic tests have returned
normal. Unusual stress, strain and fati
should be avoided for a 6-month per
following acute hepatitis. Routine laborat
follow-up study after 3 to 6 months an
year is advisable.

Other general principles of treatment
clude the institution of precautions for
pitalized patients and the administration
human immune serum globulin to those
have been heavily exposed (see Preventio

Consideration of the *role of cortisone*
ACTH in the treatment of viral hepatitis
been deferred until now because it is
lieved that the use of these agents is
visable in the usual forms of hepatitis w

progressively toward spontaneous re-
y. However, evidence available to date
ites that the proper use of these agents,
other stronger contraindications do not
affects favorably the course of viral
itis.[9, 15, 19, 31, 74, 76, 85] However, the in-
ce on the average spontaneously recov-
infection apparently is not sufficient
stify routine use because of the inci-
e of adverse effects from these drugs.
n those infections which are unusually
e, in those with delayed recovery or
se, in the cholangiolitic types with pro-
ed jaundice, and probably in the early
nic forms, the use of these agents ap-
to be capable, at times, of prompt
tion of progressive recovery. The dos-
has not yet been well established, and
ppears probable that different dosage
dules may be indicated according to the
of complication of viral hepatitis that
ing treated. It appears to be agreed gen-
y that cortisone therapy should not be
ated unless it is intended to continue
therapy until maximum improvement
been obtained. Thus premature discon-
ation of such treatment seems to have
associated with a tendency to relapse.
ppears that the cholangiolitic forms with
onged jaundice and those with delayed
very will obtain a favorable result with
tively small doses of cortisone, for ex-
le, with maintenance doses ranging from
to 10 mg. daily after 3 to 10 days of somewhat higher dosage initially. Recently, it has been suggested that massive dosage in the order of 600 to 1000 mg. of cortisone daily is beneficial in the fulminant form with precoma or hepatic coma.[19] Sufficient data are not yet available to confirm the preliminary observations in this respect. It is the author's opinion, from his personal experience to date, that cortisone and ACTH are capable of influencing favorably the course of complicated forms of viral hepatitis.

However, only further study will delineate the exact types that will be benefited and clarify the dosage schedule required. When these agents are used, the same precautions employed in their use in other conditions must be followed. Thus, salt restriction may be necessary, potassium supplementation indicated, and a careful daily search for possible adverse effects carried out. Before using these drugs, a careful historical inquiry and a gastro-intestinal series is desirable to eliminate those patients who may have an associated peptic ulcer, particularly if the indication for the use of cortisone is not such that heroic therapy, regardless of the risk, can be justified. Careful electrolyte control is essential in these patients. Recent experience suggests that prednisone (metacortandracin) may have the same beneficial effect as cortisone and ACTH without the disadvantage of the strong sodium and water-retaining effects of the latter two agents.

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Chapter 12

TOXIC HEPATITIS

Gerald Klatskin, M.D.

General Considerations

DEFINITION

Traditionally, toxic hepatitis has been defined as the type of liver injury caused by chemical agents, or by endogenous toxins presumed to be present in certain extrahepatic diseases. However, as the basic mechanisms governing the actions of these substances have been elucidated, it has become apparent that the lesions they produce by no means constitute a homogeneous group, so that it has been proposed that the various types of hepatitis encountered be classified on the basis of their pathogenesis. For the same reason it has been suggested that the term "hepatotoxin" be restricted to agents that damage the liver by a direct action on the parenchyma, and that the others be designated as sensitizing or trophopathic agents, depending on their effects. Certainly, this would serve to emphasize the mechanism of injury in each instance and thus provide a more rational basis for therapy and prophylaxis. However, our knowledge is still too fragmentary to permit such precise classification in all instances, so that the nonspecific designation "toxic hepatitis" is likely to be retained for some time. It should be noted that the term is used in its broadest sense to describe not only inflammatory reactions but also degenerative and regenerative changes in the liver.

Use of the term "toxic jaundice" should be discouraged. It not only fails to indicate whether the underlying mechanism is hepatic or hemolytic but, in overemphasizing the importance of jaundice, tends to divert attention from the fact that many agents are capable of injuring the liver seriously with producing jaundice.

PATHOGENESIS

There appear to be at least 4 ways which chemical or other toxic agents produce liver injury: (1) by direct attack the parenchyma, giving rise to what Hi worth[173] has termed "toxipathic hepatiti (2) by evoking a hypersensitivity react involving the liver, (3) by diverting, otherwise blocking, essential nutriments the internal environment, thereby produc a conditioned or intrinsic nutritional d ciency and giving rise to what has b termed a "trophopathic hepatitis"[173] (4) by providing a means for the accide transmission of the hepatitis virus during administration of therapeutic agents by parenteral route. In addition to these b mechanisms, there are several impor factors which modify the effects of hep toxins. Among these may be mentio (1) individual susceptibility, (2) circula changes, (3) the nutritional status, (4) synergistic action of alcohol, infection anoxia and (5) the presence of pre-exi liver disease.

TOXIPATHIC HEPATITIS

Most industrial agents and a few o drugs that produce hepatic injury are hepatotoxins in the sense that they are toplasmic poisons with a special affinit the liver. Characteristically, the lesions liver exhibit a distinctive pattern for ea the agents, can be induced regularly in ll, species, and make their appearance relatively brief latent period. In many es, hepatotoxins are also capable of ng other organs. Carbon tetrachlor- osphorus and chloroform may be cited cal examples in this group.

e is known about the fundamental s that occur in the cytoplasm of the hymal cell when it is exposed to a toxin. Almost 50 years ago Wells[417] ted that cellular injury and death were nsequence of inactivation of essential ive enzyme systems, leading to cessa- f anabolic processes and ultimate dis- n of cytoplasm by autolytic enzymes. concept has undergone surprisingly change over the years, and, on the the results of more recent studies lend rt to it.

ITIS DUE TO DRUG HYPERSENSITIVITY

drugs are true hepatotoxins, yet, oxically, many are capable of injuring er. The features that characterize this of hepatic damage and serve to distin- it from that produced by hepatotoxins e the following: (1) hepatitis occurs y a small proportion of individuals ex- ; (2) neither the incidence nor the ty of the injury can be correlated with nount of drug consumed; (3) the lesion reproducible in experimental animals; he onset of hepatitis bears no constant oral relationship to the institution of therapy, appearing with dramatic sud- ss after the first dose in some individu- and only after prolonged therapy in s; and (5) morphologically the lesions ariable, lacking distinctive features and form pattern.

ese characteristics clearly indicate that pe of hepatitis under discussion repre- an unusual reaction and not an nced response to one of the well-recog- pharmacologic actions of a drug. re the nature of drug hypersensitivity fully understood, such reactions were dered as manifestations of an idiosyn- , a nonspecific term implying a titutional peculiarity. However, it is reasonably certain from the work Landsteiner,[203, 204, 205] Rich[318, 319] and others[390, 414] that they are allergic in nature and are based on an acquired hypersensitivity. It has been shown that simple chemical compounds are capable of serving as antigens and inducing hypersensitivity,[203, 390] and that the tissue changes in experimental anaphylactic reactions closely resemble those produced by drug sensitization.[166, 321] The similarity of the manifestations in drug reactions and serum sickness, and the evidence supporting their common pathogenesis have been reviewed by Longcope[231] and Chase[61] and need not be reiterated. Suffice it to say that a preponderance of evidence points to an acquired hypersensitivity as the basis for most, if not all, drug idiosyncrasies. Nevertheless, some aspects of such reactions appear to be inconsistent with this concept. These include the rarity with which circulating antibodies and skin hypersensitivity can be demonstrated, the inconstancy of the interval between the first exposure to a drug and the development of a reaction, and the variable character of the clinical manifestations. In contrast, the anaphylactic type of hypersensitivity, which is presumed to be responsible for serum sickness, is characterized by the presence of demonstrable circulating antibodies and skin sensitivity, an immediate reaction to the antigen in the sensitized host, and a response that is distinctive for the species.[320] Even in the delayed or tuberculin type of hypersensitivity, the interval between the injection of an antigen and the appearance of a reaction in a sensitive host is usually not longer than 24 to 48 hours, and skin hypersensitivity can be demonstrated with great regularity.[320] At the present time our knowledge is too fragmentary to account for these discrepancies, although several possibilities may be considered. Since simple chemical compounds require conjugation with protein before they can serve as antigens,[204, 205, 414] it is conceivable that variations in the length of the latent period are related to differences in the speed with which such conjugates are formed, and that failure to demonstrate circulating antibodies and skin hypersensitivity may be due to the use of inappropriately conjugated antigens in testing. Differences in the metabolic pathways followed by drugs may determine the readiness with which antigens are produced and, hence, account for variations in individual susceptibility. Although drug reactions occur more frequently in individuals with an allergic background, it is difficult to attribute differences in susceptibility to hereditary constitutional factors alone, since the vast majority of reactions occur in individuals with no such background.

The feature of drug hypersensitivity most difficult to explain is the extreme variability of its manifestations. Why such hypersensitivity is expressed as a fever and a rash in one individual, as a hepatitis in another, and as a depression of myelopoiesis in a third, or why some drugs produce one or another of these manifestations more frequently than any of the others is completely unknown. Certainly in experimental anaphylactic hypersensitivity there is far less individual variation, and the nature of the sensitizing agent plays no significant role in determining the character of the reaction. Since the lesions are thought to be the consequence of an antigen-antibody reaction on or within cells,[166] it has been suggested that the manifestations of hypersensitivity depend on the distribution of antibody within the tissues. Actually, however, it is clear from the studies of Rich[320] and his associates[48, 115] that the injury produced by the anaphylactic type of hypersensitivity reaction is confined to the blood vessels and smooth muscle, so that it must be assumed that there is a selective localization of either antigen or antibody in these tissues to account for the distribution of the lesions.

Closely related to this problem is the question of how the hepatic lesions in drug hypersensitivity are produced. Buckley[48] and Follis[115] have presented convincing evidence to show that the hepatic cells do not participate in anaphylactic reactions, and that the focal necrosis and inflammation that occur in the liver[163, 230] are almost certainly secondary to vascular injury. Similar hepatic lesions have been described in a few cases of drug hypersensitivity,[122] but in the vast majority the nature of the lesions suggests a direct injury to the parenchyma. This raises the question of whether drug reactions may not be more closely related to the delayed tuberculin type of hypersensitivity, the type usually due to infection, and characterized b sensitization of the tissues generally and b absence of demonstrable circulating ant bodies. Chase,[61] who has studied this prob lem carefully, believes that on the basis available experimental evidence it is highl probable that both the immediate anaphy lactic and the delayed tuberculin types hypersensitivity reaction occur in drug sens tization. However, it should be pointed ou that the immunologic aspects of drug hype sensitivity in man are poorly understood, an that, at least with respect to the usual ab sence of skin sensitization, they differ fro those in experimental animals. Moreove few of the striking clinical manifestations drug hypersensitivity have been reproduce experimentally. It would seem reasonabl therefore, to consider drug reactions as man festations of a unique type of hypersensiti ity, at least until such time as their relatio ships to the other known varieties have bee defined more clearly.

Two generalizations are worth bearing mind. First, if a drug produces liver inju in man but fails to do so in other specie it is likely to be a sensitizing agent. Secon if it gives rise to any other manifestations hypersensitivity, it can be predicted that probably will produce hepatitis in som cases.

Trophopathic Hepatitis

In animals, it is possible to produce ma sive necrosis of the liver by means diets deficient in sulfur-containing ami acids.[138, 172] This has led to the concept th lesions of this type are the direct cons quence of a specific nutritional deficien and, therefore, should be classified as troph pathic. Himsworth, the principal propon of this view, has brought forward eviden to implicate cystine as the essential de ciency[138] and has suggested that this m follow not only dietary restriction but a excessive losses and increased demands cystine.[171] It is in this connection that so of the hepatotoxins are thought to play role. Thus, it has been suggested that massive necrosis and postnecrotic scarr that follow exposure to trinitrotoluene the result of a deficiency created by the co bination of cystine with free nitrous grou

plicated by an increased demand for
ne due to a rise in the metabolic rate.[171]
larly, the hepatic lesions produced by
nic selenium poisoning in animals have
attributed to an induced cystine defi-
cy related to the replacement of sulfur
selenium in sulfhydryl amino acids.[171]
ording to Himsworth,[173] the same type
conditioned cystine deficiency may be
ponsible for the massive necrosis that oc-
onally supervenes in toxipathic hepatitis.
e the deficiency is believed to be the con-
uence of a circulatory disturbance within
liver leading to ischemia.

Considerable doubt has been cast on this
cept by the discovery that the diet must
lacking in both cystine and tocopherol
the experimental production of massive
rosis, and that either substance alone is
able of preventing the lesion.[152, 153, 174]
örgy, one of the first to point out the
onsistency involved in a specific nutri-
nal defect that is preventable by two
mingly unrelated substances, has sug-
ted that cystine and tocopherol may act
detoxifying agents, and that in their ab-
ce the liver is injured by endogenous
atotoxins, generated by bacteria in the
estinal tract.[153] In support of this hypothe-
he has shown that chlortetracycline
ureomycin), in doses sufficient to suppress
intestinal flora, protects the liver to some
ent against dietary necrosis.[155] However,
possibility that the protective action of
lortetracycline is unrelated to its antibiotic
ect has not been completely excluded. To
d to the complexity of this problem,
hwarz[346, 347] has shown recently that ex-
rimental dietary necrosis is dependent on
deficiency not only of tocopherol and
stine but also of a third factor, a water-
luble, acid-stable but otherwise unidenti-
d substance which he has isolated from
sein.

On the basis of a critical review of the
erature on the interrelationships between
e effects of hepatotoxins and certain die-
ry factors, Drill[85] has suggested that it is
ghly probable that a common mechanism
nderlies the hepatic damage produced by
stine and tocopherol deficiency on the one
and, and by some of the hepatotoxins on
e other. He points out that in both instances there appears to be a reduction in available sulfhydryl groups, due either to inadequate stores or to chemical inactivation, and that as a result there is interference with certain of the intracellular enzymatic oxidation-reduction systems. However, since there is no conclusive evidence at the present time that any of the hepatotoxins induces a specific nutritional deficiency in man, there is little justification for classifying any type of human hepatitis as trophopathic.

ACCIDENTAL TRANSMISSION OF VIRAL HEPATITIS

It is now well known that the hepatitis virus can be transmitted by means of improperly sterilized syringes contaminated with blood, and that this constitutes one of the hazards of parenteral therapy. This has occurred most frequently following the administration of arsenicals,[236] insulin[356] and penicillin,[178] but there is, of course, no reason to believe that these are the only agents capable of serving as vehicles for the hepatitis virus. It is important to bear this possibility in mind in evaluating the hepatotoxic effects of therapeutic agents. The occurrence of hepatitis during prolonged parenteral therapy, or after an extended latent period, should arouse suspicion of a syringe-transmitted viral infection. A number of drugs, still classed as hepatotoxins by most authors, probably fall into this group. Thus, hepatitis has been described as a toxic complication of therapy with bismuth salts,[283] some of the antimonials[278] and liver extract,[100] agents that ordinarily do not produce liver injury in animals. Of special significance is the fact that the disease has occurred invariably in individuals undergoing group therapy in dispensaries or hospitals and has appeared late in the course of treatment, or after a long latent period—features strongly suggesting a syringe-transmitted type of viral hepatitis.

INDIVIDUAL SUSCEPTIBILITY

The striking differences in individual susceptibility to the sensitization type of drug hepatitis seldom can be explained. Occasionally, an allergic background, previous sensitization to other drugs, or intermittence of therapy appears to play a role, but in the vast majority of cases the occurrence of hepatitis cannot be correlated with any of these factors or with the amount of drug consumed. In contrast, there are few variations in individual susceptibility to the true hepatotoxins that cannot be ascribed to age differences, the route of administration, or other exogenous factors, such as antecedent diet, alcohol intake or associated infection.

Vascular Factors

Alterations in the intralobular circulation and vessel walls probably play an important role in the pathogenesis of both toxipathic and drug hepatitis. Exposure to carbon tetrachloride, for example, produces an immediate but transient intralobular vasoconstriction, which, as the exposure continues, is followed by a more sustained obliteration of the sinusoids due to swelling of the parenchymal cells.[404] Since the subsequent centrilobular degenerative changes and necrosis occur in areas where the circulation is most restricted,[137] it is reasonable to suppose that they are the result of ischemia. Whether the ischemic effect is due to anoxemia, or to a reduction in circulating sulfhydryl amino acids, is not known, but the former seems to be more likely, since anoxemia per se is capable of producing similar lesions,[245] while sulfhydryl amino acid supplements do not prevent their occurrence.[86] Agents like allyl formate, which cause dilatation of the sinusoids without any impairment of circulation, characteristically produce peripheral rather than centrilobular necrosis.[333] Observations like these suggest that, although the maximum direct effect of an hepatotoxin is exerted at its point of entry at the periphery of the lobule, the concentration attained in this area may, in some instances, be insufficient to produce necrosis and merely causes cellular swelling with a secondary impairment of blood flow which leads to centrilobular necrosis.

There is also evidence to indicate that some agents exert their deleterious effects on the liver by injuring blood vessels. In urethane poisoning, for example, parenchymal damage is secondary to changes in the portal veins and sinusoidal capillaries which lead to extravasation of plasma and red cells.[83] Similarly, the hepatic lesions in senecio poisoning[330, 351] and following massiv doses of arsphenamine[196] appear to be related to vascular thromboses. It is conceivable, therefore, that vascular damage may pla a role in the pathogenesis of other types o toxipathic hepatitis which have not bee investigated as carefully.

There seems to be little doubt that at leas some of the hepatic lesions seen in hypersensitivity reactions are related to vascula injury. In experimental anaphylaxis, for example, infarction of the liver may follow th development of periarteritis and thrombosi of the hepatic artery.[321] Similarly, in dru reactions, granulomatous and other inflammatory lesions are often found in clos proximity to necrotic vessels in the port triads,[122, 271] suggesting an etiologic relatio ship. Whether the other hepatocellul changes seen in drug reactions are secondar to endothelial damage and altered perm ability of the sinusoids, as suggested b Rich,[320] is still a moot question. Certainl the histologic changes observed in exper mental anaphylactic shock in the dog[4] would appear to strengthen this possibilit However, these findings have not been co firmed in other species,[163] and obvious va cular lesions in the liver are not alwa demonstrable in human cases of drug hype sensitivity.

Nutritional Factors

The susceptibility of animals to hepat toxins is influenced greatly by their nut tional status, and clinical experience sugges that the same may be true of man, althou the evidence is not nearly as convincing. general, starvation and high-fat diets e hance, while high-carbohydrate and hig protein diets protect against the hepatoto effects of these agents. It should be emph sized, however, that there are exceptions this generalization and that in the case many hepatotoxins the effects of diet are known. Moreover, the results of changin single dietary constituent are difficult interpret unless due consideration is given concomitant changes in the other com nents and caloric value of the diet, and their effect on net food intake, factors wh

quently have been neglected in toxicity
dies and probably account for some of
apparent inconsistencies reported.

Even a relatively brief period of starvation
reases the severity of the hepatic damage
oduced by chloroform[78] and carbon tetra-
oride.[117] High-fat diets enhance their
icity to even greater extent.[39, 286] In con-
st, carbohydrate appears to protect the
er against injury by these and other
ents.[39, 286] The effects of protein are vari-
le, depending not only on the nature of
e hepatotoxin but also on other factors.
hus, protein deficiency increases the sus-
ptibility of the liver to chloroform[266] but
t to carbon tetrachloride.[88] As might be
pected, therefore, a high-protein diet pro-
cts the liver against chloroform injury,
pecially in the protein-depleted animal,[265]
t not against the damage produced by car-
n tetrachloride[88] and many other agents.[85]
s protective action also depends in part on
e nutritional status. Thus, protein supple-
ents are far more effective in preventing
loroform injury in the depleted animal[265]
an they are in the animal with normal pro-
in stores.[78] The source of protein is another
ctor that may influence the results. Meat,
r example, in contrast with other proteins,
tually enhances the toxicity of some
ents,[38] an effect which appears to be re-
ted to the presence of toxic nonprotein
trogenous compounds.

Other dietary constituents are of interest
connection with toxic hepatitis not only
r their possible therapeutic value but also
r the clues that they may provide to the
echanisms involved in the actions of he-
atotoxins. Of these choline, methionine,
ystine and tocopherol have received the
reatest attention.

Choline accelerates the removal of excess
t deposited in the liver as a result of carbon
trachloride[16] or phosphorus poisoning[33]
ut does not prevent liver damage. Methio-
ine, on the other hand, appears to protect
gainst chloroform toxicity both in protein-
epleted[266] and stock-fed animals.[47] How-
ver, it is still not certain that the site of this
ction is in the liver. In carbon tetrachloride
oisoning, for example, methionine increases
he survival time of animals on low-protein
diets by preventing renal necrosis[154] but does not protect the liver.[87] In conjunction with alpha-tocopherol supplements, methionine also appears to be protective in selenium poisoning but fails to prevent cirrhosis when given alone.[350] It is of interest in this connection to note that alpha-tocopherol alone protects against carbon tetrachloride toxicity in rats on low-casein diets.[176] However, prolongation of survival in this instance probably is not due to any hepatic effect, since liver damage is not prevented.[177]

Cystine has not been studied as extensively as the other dietary constituents mentioned. It affords some protection against the hepatotoxic effects of chloroform in the protein-depleted dog but is inferior to methionine in this respect[265] and has no effect in other forms of toxic hepatitis.[85]

Dietary factors appear to exert their influence on the susceptibility to hepatotoxins by altering either the fat content of the liver or the size of the protein stores. In general, susceptibility is enhanced by measures that lead to an increase in hepatic fat or depletion of protein and is reduced by those that produce the reverse changes.[143] The heightened susceptibility associated with fatty infiltration of the liver is thought to depend, in some instances at least, on the solubility of hepatotoxins in fat.[85, 143] Obviously, this cannot account for the increased toxicity of agents that are relatively insoluble. As for the enhanced susceptibility to hepatotoxins related to the reduction in protein stores, it has been suggested that the interaction of such agents as chloroform with sulfhydryl amino acids leads to a rapid depletion of the latter in essential enzyme systems in the liver. A decrease in available protein also may exert a deleterious effect by retarding the regeneration of injured cells, a factor that has been little studied. At one time the glycogen concentration was thought to be the major factor that determined the susceptibility of the liver to injury, a concept that was responsible for the widespread adoption of high-carbohydrate diets in the therapy of hepatic disease. However, it is now known that the susceptibility to hepatotoxins is not related to the glycogen content of the liver, and that the protective action of carbohydrate depends on its protein-sparing effect and a reduction in hepatic lipids.[143]

Synergism

There is convincing experimental evidence to indicate that ethyl alcohol enhances the hepatotoxic effects of chloroform,[331] carbon tetrachloride,[200] phosphorus[112] and certain other chlorinated hydrocarbons,[28] without itself producing any appreciable liver damage. It may be of significance that all of these agents are highly soluble in fat solvents, which has led to the suggestion that alcohol, by serving as a vehicle, may either increase their absorption from the intestinal tract or facilitate their penetration and storage in cells.[331] Clinicians have long suspected that alcohol also enhances the effects of other hepatotoxins. However, there is no conclusive evidence of this; indeed, the only clear-cut instances of such synergism in man have been found in cases of carbon tetrachloride poisoning.[269, 363]

In experimental animals the injection of relatively innocuous bacteria greatly increases the hepatotoxic effects of chloroform and phosphorus and produces a type of midzonal or massive necrosis that is not seen in uncomplicated poisoning with these agents.[285] The mechanism of this action is not known, but it has been suggested that hepatotoxins may injure the vessels of the liver and thus permit organisms to gain access to otherwise protected parenchymal cells. Whether or not infection plays a similar role in man remains to be determined.

Anoxia appears to enhance the hepatotoxic effects of certain anesthetic agents,[332] but in this instance the action may be additive rather than synergistic, since anoxemia per se can produce serious liver injury.[102, 245]

Pre-existent Liver Disease

There is a clinical impression that the presence of pre-existent liver disease increases susceptibility to hepatotoxins. Almost without exception the instances reported have followed the use of drugs, suggesting that liver damage may predispose to sensitization reactions. The frequency with which other manifestations of hypersensitivity occur in individuals with chronic liver disease[294] would appear to be consistent with this hypothesis. However, there is convincing experimental evidence to show that antecedent injury to the liver also renders it more susceptible to further damage by other hepatotoxins.[28]

PATHOLOGY

Toxipathic Hepatitis

The morphologic changes in toxipathic hepatitis vary, depending on the dose, the route of administration and the mode of action of the responsible agent. In general, however, the acute hepatic lesions tend to be distributed uniformly throughout the lobules in a zonal pattern and show all stages of parenchymal degeneration from simple swelling to acute necrosis, but little or no inflammatory reaction. Fatty infiltration is usually a prominent feature. In the case of many hepatotoxins the intralobular location of the lesions is distinctive. Thus, they characteristically occur in the centrilobular zone in carbon tetrachloride[51] and chloroform[41] intoxication and in the periportal zones in phosphorus poisoning.[173] However, the distribution may vary in some forms of toxi hepatitis. Occasionally, the lesions exten beyond the limits of the lobules, giving ris to areas of massive necrosis, as, for example in poisoning with the *Amanita phalloide* toxin[91] and some of the chlorinated naphthalene and diphenyl compounds.[114] Cur ously, agents that produce zonal lesion seldom give rise to massive hepatic necrosi even when very large doses are administere In experimental animals, for example, eve lethal doses of carbon tetrachloride or chl roform fail to produce this type of lesio unless they are injected directly into the po tal circulation.[52] In general, however, t severity of the lesion and the size of the do are closely correlated.

As a rule, toxic hepatitis of the zonal ty is a self-limited disease that goes on to co plete recovery without residuals. If, ho ever, the exposure to a hepatotoxin is co tinuous, or if it is repeated at intervals t do not permit complete recovery on ea occasion, a diffuse fibrosis may ensue a terminate in a picture that closely resemb Laennec's cirrhosis.[51] When necrosis is zo regeneration proceeds in an orderly fash in the confines of an intact reticulum by iferation of the remaining viable cells in same lobule, thereby restoring the normal ilar architecture. However, this is not sible in the case of massive necrosis, e regeneration must proceed from distant ules bordering the necrotic zones. Large sses of proliferating parenchymal cells are med which compress the intervening ne- tic zones, containing intact reticulum, od vessels and bile ducts, into broad ds. This produces the condition variously cribed as toxic cirrhosis, postnecrotic rring with nodular hyperplasia and healed ssive or subacute necrosis.

Drug Hypersensitivity Hepatitis

The morphologic features in this condition even more variable than in toxipathic patitis. In general, however, the hepatic ons tend to be focal and irregular in dis- bution and are characterized by parenchy- l degeneration and necrosis, as well as intense inflammatory reaction in the por- areas. Fatty infiltration is unusual. Focal nulomata occur in some cases, especially the portal triads where the vessel walls y be involved in a similar process.[122, 271] nal lesions and massive necrosis are un- ual but occur often enough so that the tern of the lesions cannot be relied upon distinguish between the toxipathic and hypersensitivity types of hepatitis.

Complete restitution of the liver usually lows cessation of drug therapy, although recovery period tends to be somewhat nger than in toxipathic hepatitis. As might expected, massive necrosis is followed by rring. Occasionally, hypersensitivity re- tions give rise to a chronic hepatitis aracterized by an intense, predominantly nonuclear infiltration of the portal zones th relatively little change in the parenchy- al cells. As the disease progresses there is placement of the parenchyma by extensions the portal exudate and fibrosis. The writer s seen a number of such examples appar- tly due to reactions to sulfonamides, thio- ea and phenobarbital.

There is another type of hypersensitivity action in the liver in which the parenchymal lls show little or no change. The principal dings in this condition are an intense, predominantly mononuclear inflammatory reaction around the smaller bile radicles, and marked intralobular bile stasis. Since the clinical and laboratory features also point to an obstructive rather than a parenchymatous jaundice, it has been suggested that the interlobular bile ducts are occluded by inflammatory exudate.[160] Not infrequently the disease runs a prolonged course and is accompanied by hepatomegaly, splenomegaly and hypercholesterolemia[160] and occasionally by the development of xanthomatosis.[34, 387] The syndrome has been seen most frequently in association with hypersensitivity reactions to the arsphenamines[160, 387] but has been described also following sulfonamide,[30] thiouracil[126] and neocinchophen[34] therapy. In some individuals the process appears to be slowly progressive with the development of portal fibrosis and the clinical picture of a biliary cirrhosis.[30, 34] Both the clinical and the histologic findings in such cases bear a remarkable resemblance to those described by MacMahon[239] and Ahrens[3] in primary biliary cirrhosis, a disease which, in the past, has masqueraded under a variety of other names, including xanthomatous, pericholangiolitic and nonobstructive biliary cirrhosis. Xanthomatosis, which is such a striking feature in advanced cases, is often absent early in the disease. Both the hypercholesterolemia and the xanthomatosis are now known to be secondary to the associated liver damage and not its cause.[3, 239] The etiology of this disease is not known, although some cases are thought to be due to the hepatitis virus.[410] In view of the fact that drug hepatitis may produce a syndrome that is indistinguishable from it, the question may be raised whether hypersensitivity reactions may not be responsible for many other cases classified as idiopathic or primary biliary cirrhosis.

Differentiation of Toxic from Viral Hepatitis

Descriptions of the morphologic changes in viral hepatitis[11, 81, 232, 233, 242] differ so markedly from those of toxic hepatitis that there would appear to be little reason to discuss their differentiation. Nevertheless, even experienced pathologists find it difficult to distinguish between the two in some instances.

The features that usually serve to differentiate toxic from viral hepatitis include: (1) the location of the lesions in the lobule, (2) the nature of the cytoplasmic changes in the parenchymal cells, (3) the type of regenerative response and (4) the character of the inflammatory reaction.[304]

In general, the lesions are more clearly zonal in the toxic than they are in viral type of hepatitis. However, exceptions to this generalization are so common that the intralobular location of the lesions cannot be regarded as a reliable criterion in their differentiation.

Usually it is stated that the affected parenchymal cells in viral hepatitis characteristically undergo rapid lysis, leaving few cellular remnants, so that, even very early in the disease, few if any of the remaining cells exhibit degenerative changes denoting slow death of cells.[304] An exception is the appearance in less severe cases of a characteristic type of eosinophilic hyalinization of scattered cells, giving rise to globular structures that closely resemble the Councilman bodies of yellow fever. (See Chap. 10, Pathology of Hepatitis.) In toxic hepatitis the death of cells appears to occur more slowly, so that the involved parenchyma exhibits all stages of degeneration from simple loss of basophilia to complete necrosis. Although some of the cells may contain masses of hyaline material, few undergo the type of complete hyalinization seen in viral hepatitis. Many of the cells show nuclear changes, and in some the nuclei are lost, leaving behind large cytoplasmic remnants. The presence of intracellular fat globules is an important but by no means constant diagnostic feature of toxic hepatitis. Although these differences are usually very striking in autopsy material, they are far less so in biopsy material, especially in the less severe forms of the disease. Indeed, there is evidence to suggest that the rapid autolysis of cells in fatal cases of viral hepatitis may, in part at least, be a postmortem phenomenon.[398] Certainly, biopsy specimens in nonfatal cases of viral hepatitis reveal a variety of cytoplasmic and nuclear degenerative changes that are consistent with the same type of slow death of cells seen in toxic hepatitis. Although the presence of hyalinized Councilmanlike bodies in viral hepatitis, on the one hand, and of fatty infiltration in toxic hepatitis, on the other, are helpful diagnostic features, they are by no means constant findings. Moreover, the diagnostic importance of fatty infiltration is somewhat nullified by the fact that it may occur also as a late manifestation in viral hepatitis.[180]

As might be expected from the well-known regenerative capacity of the liver, signs of active hepatocellular proliferation soon make their appearance in both types of hepatitis. However, the process is usually more active in the viral type. Characteristically, the regenerated cells in this disease show marked variations in size, staining qualities and organization. In contrast, the replacement of the necrotic cells in toxic hepatitis appears to proceed at a more leisurely pace, so that the regenerated areas are usually relatively normal in appearance. Mitoses are infrequent in both types of lesion, except immediately after injury. Bile duct proliferation also appears to be more active in viral than in toxic hepatitis.

The inflammatory reaction in viral hepatitis is highly characteristic, and usually can be distinguished from that of toxipathic hepatitis. There is a diffuse intralobular proliferation and swelling of the reticuloendothelial system, and a striking mononuclear cell infiltration of the entire lobule, most marked in the necrotic areas and the portal zones. Phagocytic monocytes predominate and, in the necrotic areas where they are most numerous, many contain large amounts of yellow pigment. Lymphocytes, plasma cells and eosinophils constitute the remainder of the inflammatory exudate. In contrast, the inflammatory reaction in toxic hepatitis is relatively slight. Reticuloendothelial hyperplasia is minimal, the intralobular exudate is often polymorphonuclear in nature, and pigment deposits are unusual. The inflammatory reaction in drug hepatitis may be indistinguishable from that of viral hepatitis, especially in the more chronic form of the disease. However, the presence of focal granulomata and vascular lesions may serve to differentiate the two.

RELATION TO ACUTE YELLOW ATROPHY

Since the first description of acute yellow atrophy in 1842, pathologists have debated over the specificity of its etiology and morphology. There is general agreement, however, that the term is misleading, since the essential lesion is a massive necrosis of hepatic cells and not an atrophy. As for the color of the liver, it may be red or yellow, depending on the stage of the disease. Moreover, the lesion is not always an acute one, subacute and chronic forms being well recognized.[328] Major differences of opinion exist over the question of whether the term should be restricted to the idiopathic type of massive necrosis, now known to be a manifestation of viral hepatitis,[65, 232, 432] and whether the morphologic features in the viral type can be distinguished from those due to drugs and poisons.

Very early it was recognized that massive necrosis of the liver occasionally followed sepsis, toxemia of pregnancy and certain poisonings, but that in most cases no etiologic factor could be demonstrated.[168] In a remarkable paper written in 1912, Cockayne[65] first called attention to the probable relationship of these idiopathic cases to infectious hepatitis, a disease whose viral etiology had not yet been demonstrated, but whose infectious nature he recognized. There can be little doubt now that most instances of acute yellow atrophy are due to viral hepatitis.[81, 232, 233, 432] Many authorities[232, 233, 328] believe, moreover, that the morphologic features in this group can be differentiated readily from those in other types of massive necrosis. The rapidity and the completeness of cellular autolysis, the absence of fatty change and coagulation necrosis, and the character of the inflammatory reaction have been stressed as characteristic features of the viral type. However, they may be simulated by trinitrotoluene intoxication[384] and hypersensitivity reactions to cinchophen[25] and sulfonamides,[271] so that they cannot be relied upon in distinguishing between toxic and viral massive necrosis. The absence of regeneration in the toxic type[25, 271] has also been emphasized as a point of difference, but the same feature has been observed in the fulminant form of viral hepatitis.[233]

MECHANISM OF JAUNDICE

Retention of bilirubin secondary to hepatocellular injury would appear to be the most likely cause of jaundice in toxic hepatitis. However, it has been suggested that bilirubin also may be regurgitated into the blood or the lymph through ruptured canaliculi or abnormally permeable cholangioles, a hypothesis based on the observation that a considerable fraction of the serum bilirubin diazotizes promptly in the direct van den Bergh reaction, and that the urine often contains bile. The interpretation of the van den Bergh reaction in terms of the mechanism of jaundice is still a matter of dispute,[191] so that the regurgitation of bile in toxic hepatitis cannot be regarded as an established fact. Autopsy evidence of communications between the canaliculi and the perisinusoidal spaces has been cited also in support of the hypothesis of regurgitation.[439] However, it has been shown that these are agonal in character and are not present in biopsy specimens.[302] Moreover, the impression that such communications occur is based on the assumption that double columns of hepatic cells constitute the walls of the canaliculi, and that hepatocellular necrosis interrupts their continuity. However, it is now known that the canaliculi comprise a rich branching network of rigid tubes that do not depend on the parenchyma for support, and that the parenchymal cells are arranged in fenestrated laminae one-cell thick.[99] It is highly improbable, therefore, that the loss of cells results in leakage of bile from the canaliculi. So far as the factor of increased permeability of the cholangioles is concerned, it cannot be excluded with certainty, but there is no direct evidence to prove its existence.

An obstruction of the interlobular cholangioles by inflammatory exudate has been postulated to account for the jaundice seen in the hypersensitivity type of arsenical hepatitis.[160] It is difficult to prove or disprove this hypothesis, but the fact that the same type of exudate occurs in other forms of hepatitis without producing obstruction is certainly a point against it. In the case of methyl testosterone hepatitis, jaundice has been attributed to obstruction of the central canaliculi by bile thrombi,[418] a highly improbable explanation in view of the fact that the canaliculi are arranged in an endless mesh which could hardly be obstructed by scattered plugs of inspissated bile. The absence of histologically demonstrable changes in the parenchymal cells in both these conditions does not exclude the possibility of a functional impairment of bilirubin excretion, and, indeed, this would appear to be the most likely explanation for the jaundice.

RELATION TO HEPATOMAS

Prolonged exposure to a number of hepatotoxins, including carbon tetrachloride[98, 107] and selenium,[281] is known to induce hepatomas in experimental animals. Although cirrhosis usually precedes the appearance of these tumors, it is not known whether necrosis and regeneration of parenchymal cells are essential for their development.[107] Theoretically, at least, hepatotoxins should be capable of inducing hepatomas in man. However, no authenticated cases have been reported.

CLINICAL FEATURES

LATENT PERIOD

Characteristically, the clinical manifestations of hepatic injury do not become evident for a variable interval following exposure to hepatotoxins.

In acute toxipathic hepatitis, due to such agents as carbon tetrachloride and chloroform, the latent period is relatively brief, usually not exceeding a day or two, and is well correlated with the evolution of the lesion microscopically. Although histologic signs of hepatocellular injury appear within a few hours, necrosis does not reach its maximum for a period of 48 hours.[51, 419] This delay is thought to be related to the progressive impairment of the intralobular circulation that follows the initial swelling of the parenchymal cells.[137]

Following repeated exposures to relatively small doses of certain hepatotoxins there may be a long interval before signs of cirrhosis become clinically evident.[299] This does not constitute a period of true latency, since it is possible to demonstrate the presence of progressive lesions histologically at a very early stage.[51] The delayed appearance of symptoms in this instance is probably related to the fact that slowly progressive lesion
are usually accompanied by compensator
parenchymal hyperplasia.

The most striking examples of delaye
hepatitis are seen in sensitization reactions
Here the signs of acute liver injury may no
appear until a drug has been administered fo
a period of many months. In some cases
however, the latent period is relatively brief
In arsphenamine hypersensitivity, for ex
ample, hepatitis characteristically appear
after the second or the third injection.[1
Similarly, in individuals previously exposed
administration of a drug may provoke a
immediate reaction.[29] It is reasonable
suppose that the latent period in this type
hepatitis corresponds to the interval durin
which sensitization develops. Occasionall
hepatitis appears following the first dose
a drug in a previously unexposed indivi
ual.[212] It is difficult to account for such cas
unless it is assumed that inadvertent exp
sure to the drug or to some chemically relat
agent has occurred in the past.

The most striking period of latency is
one that precedes the onset of syringe-tra
mitted viral hepatitis. Here the manifes
tions become evident, either during
course of prolonged drug therapy or at so
interval thereafter, depending on the date
infection and the length of the incubat
period. In general, the latter ranges betw
2 and 4 months, so that if hepatitis appe
late in the course of parenteral drug admi
tration, or during the following 4 months
must be regarded as viral in origin u
proved otherwise.

The delayed appearance of hepatitis
lowing exposure to trinitrotoluene has ne
been adequately explained. Although s
of liver injury may appear as early as
first week, they usually occur following m
weeks of exposure.[227, 246, 384] These va
tions may be related to differences in i
vidual susceptibility and the nature of
exposure or to cumulative toxic effects. H
ever, they cannot account for the cases
occur many months following the last e
sure to trinitrotoluene.[173, 425] One pos
explanation is that a slowly progressive le
is initiated during the period of exposure
does not become clinically evident unti
advanced.

SYMPTOMS

t is important to recognize that not all of clinical features in toxic hepatitis are the sequence of liver injury; many are related he extrahepatic pharmacologic and toxic cts of hepatotoxins. In many instances it lifficult to distinguish between these two ups of symptoms, and occasionally those extrahepatic origin predominate. Signs of al damage and gastro-intestinal irritation especially common. In drug hepatitis the ns of liver injury are often accompanied other manifestations of hypersensitivity, h as fever, rash, arthralgia, adenopathy d signs of renal and hemopoietic injury.

The clinical picture of acute toxic hepa- s closely resembles that of viral hepatitis. eicteric fever and constitutional symptoms rare in toxipathic hepatitis but often cur in drug hypersensitivity reactions. orexia, nausea and vomiting are the ncipal symptoms, and jaundice and hep- omegaly are the major physical findings. a rule, the jaundice is accompanied by irubinuria, and in more severe cases, pecially of the hypersensitivity type, by le or even acholic stools and pruritus. In ld cases, on the other hand, jaundice may t become clinically evident, so that liver ury may be overlooked.

In general, recovery occurs more rapidly acute toxipathic hepatitis than in viral patitis, and residuals are less common. owever, in drug hypersensitivity reactions, e course tends to be more prolonged and, some instances, becomes chronic, leading a picture that closely resembles primary liary cirrhosis. (See Chap. 16, Biliary Cir- osis.) Even in cases that do not progress in is manner, the clinical and laboratory anifestations often suggest an extrahepatic liary obstruction. It should be emphasized, owever, that drug reactions occasionally ve rise to serious progressive inflammatory sions in the liver that terminate in cirrhosis ithout producing jaundice. Therefore, in vestigating atypical forms of cirrhosis, seri- us consideration always should be given to e possibility of previous drug sensitization. Ioreover, individuals who have had such eactions should be followed carefully and hould be protected against further exposure the offending agent.

Although a single exposure to a hepatotoxin rarely leads to permanent hepatic damage, multiple exposures, especially if repeated at brief intervals, may produce cirrhosis. The clinical course in such cases is variable. In some, there are repeated episodes of acute hepatitis before frank signs of cirrhosis become evident, while in others the onset of cirrhosis is insidious without antecedent symptoms of acute hepatic injury. Unless the exposure to a hepatotoxin is recognized, the former may be mistaken for a relapsing viral hepatitis with posthepatitic cirrhosis, and the latter for some type of Laennec's cirrhosis.

In both toxipathic and drug-sensitivity hepatitis, hepatic necrosis is occasionally massive rather than zonal or focal. As might be expected, the clinical manifestations under these circumstances are usually more severe than in uncomplicated acute hepatitis and may include such unusual features as intense abdominal pain, coffee-ground vomitus, a rapid decrease in the size of the liver, ascites, edema, hemorrhagic phenomena, somnolence and coma. The clinical course is deceptively benign in some cases. Apparent recovery takes place despite the unrecognized occurrence of postnecrotic scarring and nodular hyperplasia, and the true nature of the lesion does not become evident until signs of cirrhosis appear months or even years later. In the most severe cases death occurs within a few days. Usually, however, the course is more prolonged and is characterized by signs of hepatic decompensation. Death ensues in a few weeks or months and is usually due to hepatic failure, hemorrhage from esophageal varices or intercurrent infection.

LABORATORY FEATURES

There is nothing characteristic about the laboratory findings in toxic hepatitis. In general, the results of liver function tests are similar to those found in other types of liver injury of comparable severity and duration. However, the changes in the serum protein pattern, especially as reflected in cephalin-cholesterol flocculation and thymol turbidity, are usually less striking than in viral hepatitis.[303] The reason for this difference is not known.

As mentioned previously, the serum alkaline phosphatase and cholesterol levels tend to be high in drug hepatitis, while the cephalin-cholesterol and thymol turbidity reactions are often within normal limits. Since the same pattern is also seen in extrahepatic obstructive jaundice and in chronic cholangiolitic viral hepatitis, it is obvious that liver function tests are of little value in distinguishing between them. The history is of the greatest importance in this connection, but in difficult cases it may be necessary to resort to biopsy of the liver or exploratory laparotomy to establish the correct diagnosis.

Although liver function tests are not very helpful in differentiating toxic from viral hepatitis, they are of great value in detecting the early signs of liver injury following known or suspected exposure to hepatotoxins, and in evaluating the severity and the progress of the lesion once it is established.

TREATMENT

Removal of Hepatotoxin

Obviously, the first step in the management of toxic hepatitis is the prevention of further contact with the offending agent. In the case of chronic exposure to toxic vapors and dusts, this entails close watch on the status of the liver and prompt removal of the individual from the contaminated environment at the first sign of functional impairment. However, in patients receiving drugs, immediate cessation of therapy is indicated even before signs of liver damage appear, if other evidence of hypersensitivity develops. It must be assumed that all such reactions are potentially dangerous, and that further exposure may lead to serious liver damage.

While it is desirable to remove any remaining traces of hepatotoxin from the intestinal tract by lavage, or by overventilation in the case of toxic vapors, such procedures are seldom successful once hepatitis has developed, because of the period of latency between exposure and the appearance of clinical manifestations.

Antidotes

A number of chemical agents are known to protect against the injurious effects of hepatotoxins in experimental animals,[85] but, on the whole, these either have not been tested or have proved to be of little value in the treatment of toxic hepatitis in man. Perhaps this failure can be attributed to the fact that in most experiments these agents have been employed prophylactically rather than therapeutically.

BAL (2-3-dimercaptopropanol) would appear to be an ideal antidote in the early management of toxic hepatitis due to compounds of gold and arsenic, since it combines both with free and tissue-bound metallic ions to form relatively innocuous, soluble thio metal complexes which are readily excreted by the kidneys. However, the results of treatment have been very disappointing.[95] This is not surprising when one considers the fac that the vast majority of cases in which BAI has been tried have been due either to gol or arsenic hypersensitivity reactions, or t inadvertent infection with the hepatitis viru during treatment. If it were possible to sep arate these cases from those of true intox cation due to overdosage, the results of BA therapy in toxic hepatitis might prove to b more encouraging.

Many other chemical agents that prote against hepatotoxins in experimental anima also contain sulfhydryl groups, so that the effectiveness has been attributed to a sul hydryl-sparing action in essential enzym systems. However, some of the nonsulfhydr analogues of these agents are also effective, so that there is still some uncertainty regar ing their mechanism of action.

Diet

The rationale for the dietary manageme of toxic hepatitis is based almost exclusive on the results of animal experiments and experience gained in the treatment of oth types of liver disease. It must be recognize therefore, that proof of the efficacy of diet therapy in toxic hepatitis rests on indire evidence, the interpretation of which is st open to question.

There can be little doubt that the expe mental studies reviewed in the section Pathogenesis have demonstrated importa interrelationships between the nutritio status and the actions of hepatotoxins. Ho ever, the question may still be raised wheth they have established the efficacy of dieta tment in toxic hepatitis. Most of these eriments have been concerned with the ience of the *antecedent* nutritional status he incidence and the severity of hepatic ry following intoxication, and not with effects of diet on the regeneration and the air of the injured liver, the major con- ration in therapy. This is an important inction, since it does not follow that a ary constituent that protects against the atotoxic effects of an agent necessarily litates recovery once such injury has urred.

The effect of protein in chloroform poison- is a case in point. Here there seems to be e doubt that protein depletion enhances icity and that protein supplements are tective, even if given some hours after osure.[266] However, there is no experimen- evidence to show that such supplements ten recovery when administered after rt signs of liver disease have appeared. reover, the protective action of most tary constituents, including protein, have n demonstrated in depleted animals, so t no conclusions are warranted regarding ir therapeutic value in well-nourished ividuals with toxic hepatitis. Also, it can- be assumed that because a dietary con- uent protects against one hepatotoxin it l necessarily do so against all. This is well strated in the case of protein which pro- ts the depleted animal against chloro- m[265] but not against carbon tetrachloride[88] oxication.

Finally, in interpreting the results of ani- l experiments, care must be exercised in tinguishing between the effects of dietary asures on survival and their effects on the er per se, since the former may be related extrahepatic factors. Thus, in the case of bon tetrachloride poisoning, methionine reases survival by preventing renal injury t has no effect on liver damage.[154]

The impressive results of dietotherapy in ennec's cirrhosis have encouraged its option in other forms of liver disease, in- ding viral and toxic hepatitis. Although s trend is not to be discouraged, since the ects of diet are still under investigation, it ould be recognized that there is no conclu- e evidence at the present time to indicate t dietary measures are effective in any type of liver injury other than those due to nutritional deficiency.

In the absence of more precise information regarding the most efficacious form of treatment in toxic hepatitis, it would seem reasonable to provide a diet rich in protein and carbohydrate on the principle that protein is required for tissue regeneration and is spared when adequate nonprotein calories are provided. Although there is no evidence that the addition of fat to a well balanced protein-containing diet exerts any deleterious effects on the injured liver, fat is tolerated less well than carbohydrate during the period of anorexia and indigestion in the early stages of hepatitis and has the disadvantage that it cannot be administered parenterally. Later, however, when the appetite improves, liberal use of fat in the form of milk, cream, cheese and eggs should be encouraged, since it makes for a more palatable diet and facilitates the maintenance of a high caloric intake, thus preventing the weight loss and the debility that so often follow an attack of hepatitis.

Obviously, from what has been said, any statements regarding the precise protein and caloric requirements in toxic hepatitis are bound to be based on personal opinion and experience rather than on well-documented evidence. With this reservation in mind, it is suggested that 90 Gm. of protein and 3,000 calories constitute an adequate dietary intake. There is no evidence to indicate that a larger protein intake is more efficacious. Recent studies in cirrhosis[295] suggest that excessive amounts may actually be harmful in that they are capable of provoking a precomatose state in individuals with severe liver injury, presumably by increasing the blood ammonia (see Chap. 9, Hepatic Coma).

In prescribing protein for the patient with toxic hepatitis, due consideration must be given to the status of the kidneys, since hepatotoxins not infrequently produce a complicating lower nephron nephrosis. In such cases, measures designed to reduce nitrogen retention and to attain a normal internal environment take precedence over the less urgent needs of the liver. This usually entails marked restriction or actual omission of dietary protein, provision of sufficient carbohydrate and fat calories to minimize endogenous protein breakdown, and careful regulation of fluid and electrolyte balance. Fortunately, the relatively brief period of protein deprivation usually required does not appear to impede recovery from the associated liver injury. Similarly, individuals with severe anorexia and vomiting who require parenteral feeding do not appear to suffer any ill effects when protein is omitted for a number of days. Although parenterally administered amino acids can be utilized in the face of severe liver injury,[96] they are often poorly tolerated, so that their use is not recommended unless the situation demands parenteral feeding for a long period of time.

From a practical standpoint it is often impossible to achieve a caloric intake of 3,000 calories during the first few days of an acute hepatitis, even if the diet is supplemented with parenterally administered glucose. This need not cause concern, since the easily attainable level of 2,000 calories usually suffices to tide the patient over this acute phase without compromising his chances of recovery or leading to any significant degree of malnutrition. There would appear to be little need for tube feeding, except in rare instances of prolonged and severe anorexia. Here the threat of daily gavage often proves to be a potent stimulus for greater co-operation on the part of the patient, so that frequent repetition of the procedure is seldom required. In the comatose patient the danger of regurgitation and aspiration of tube feedings contraindicate their use.

When all or most of the calories must be administered by the parenteral route, there is an advantage in using more concentrated solutions of glucose than are generally employed. Provided that the infusion rate is slow, concentrations of 15 or 20 per cent can be infused over long periods of time without significant losses of glucose in the urine or the development of thrombophlebitis.

In experimental animals vitamin B_{12} given *prophylactically* has been shown to protect the liver against carbon tetrachloride injury.[305] There is no evidence, however, to indicate that vitamins administered *following* toxic injury to the liver facilitate recovery. There would appear to be no rationale, therefore, for supplementing the diet in the treatment of toxic hepatitis, except possibly in instances where the antecedent diet has been deficient, or where prolonged parenteral feedings of vitamin-free glucose may precipitate an acute deficiency state.

The effects of methionine and choline in experimental animals have encouraged the use of these agents in the treatment of toxic hepatitis.[22, 97] However, quite apart from the previously discussed theoretical reasons for considering this practice illogical, there is no convincing clinical evidence to show that these dietary supplements have any therapeutic value in well-nourished individuals.

The principles governing the management of the cirrhosis that occasionally follows toxic hepatitis are essentially the same as those for Laennec's cirrhosis and, therefore, require no further discussion. However, it should be pointed out that the response to dietotherapy is likely to be far less impressive in the toxic type, since nutritional factors are either lacking or are of subsidiary importance in its pathogenesis.

BED REST

The strong clinical impression that be rest is of value in the treatment of acut viral hepatitis is based on somewhat incon clusive evidence. Even less is known abou its importance in toxic hepatitis. Neverthe less, it is generally conceded that it is prob ably wise to enforce bed rest in the patien with toxic hepatitis on the principle that i enhances hepatic blood flow and reduces th over-all metabolic demands on the liver an thus may facilitate recovery from injur Obviously, it is not possible to define pre cisely the optimal duration and degree restricted activity. Nevertheless, so long uncertainty exists, it is safer to err on the sid of conservatism and to enforce strict bed re until the patient is well on the road to re covery, certainly at least until jaundice an hepatomegaly have subsided. If laborato facilities are available it may be wise to wa until the serum bilirubin level has fallen 2 mg. per cent and bromsulphalein retentio to 10 per cent or less before allowing th patient out of bed. It is of equal importan to watch the patient carefully for the wee or two following resumption of activity an to reinstitute bed rest if clinical or chemic pse occurs. In dealing with the more nic forms of hepatitis, particularly those 1 in hypersensitivity reactions, strict ad- ence to these criteria may prolong con- scence to no advantage. For that reason s recommended that ambulation be re- ed if the clinical and functional status of liver remains stationary for a week or . If resumption of activity does not ag- vate the hepatitis, it is reasonable to as- e that further bed rest will be of no efit.

ACTH AND CORTISONE

In view of the remarkable effects of ACTH l cortisone in allergic reactions in general, s highly probable that they will prove to of value in the treatment of severe hepa- s due to drug hypersensitivity. There is no nvincing evidence to indicate that these nts significantly alter the clinical course the average case of viral hepatitis, so that s unlikely that they will do so in toxipathic patitis. However, they occcasionally serve useful adjuncts in overcoming the malaise, the anorexia and the vomiting of severe viral hepatitis and thus tide the patient over a difficult period. Moreover, there have been reports of recovery from the fulminant type of viral hepatitis following massive doses of these agents,[93] suggesting that occasionally they may be lifesaving in cases with massive necrosis. It may be justifiable, therefore, to try these agents in gravely ill cases of toxipathic hepatitis.

DESENSITIZATION

Drugs that have produced hepatitis are occasionally deemed sufficiently important in subsequent therapy to warrant an attempt at desensitization. Only rarely, however, is this successful, and since the danger of provoking a serious reaction is great, even with the small doses employed, it is generally considered unwise to attempt the procedure except under unusual circumstances. In urgent cases the concomitant administration of ACTH or cortisone may make it possible to resume drug therapy without precipitating a second hypersensitivity reaction.

Special Features of Agents Capable of Producing Liver Injury

Hepatotoxins comprise such a hetero- neous group with respect to their chemical ucture and mode of action that they are ficult to classify in any logical or orderly anner. It is purely as a matter of conven- ice, therefore, that a simple alphabetical rangement is employed in the following ction. The agents selected for discussion no means constitute a complete inventory substances capable of injuring the liver, t the list includes most of those known to oduce toxic hepatitis in man.

ACCIDENTAL AND INDUSTRIAL POISONING

BERYLLIUM

Inhalation of beryllium compounds may ovoke either an acute pneumonitis or a ronic granulomatous reaction in the lung. e former, which is more common, follows exposure to most of the beryllium dusts and fumes encountered in industry, appears after a relatively brief incubation period, is characterized pathologically by an exudation of mononuclear cells into the alveoli, and usually undergoes complete resolution within a period of 4 months. In contrast, the chronic disease develops almost exclusively following exposure to beryllium oxide, appears only after a long incubation period, is characterized pathologically by a diffuse granulomatous reaction that closely resembles sarcoidosis, and runs a chronic progressive course that often terminates fatally.[382, 400] Although the two conditions are usually regarded as distinct clinical and morphologic entities, it has been suggested, on the basis of autopsy studies, that the granulomatous lesion may represent a late development in the evolution of the acute pneumonic process.[94] However, this view is not supported by either experimental[386] or epidemiologic[382] evidence. It has been possible to reproduce the acute pneumonic process in animals by exposing them to an atmosphere containing a high concentration of beryllium,[386] but in no instance has either the inhalation[386] or the parenteral administration[348] of beryllium resulted in granuloma formation. Sterner and Eisenbud[382] have recently reviewed certain epidemiologic evidence which suggests that the granulomatous reaction in the lung may be due to sensitization, in contrast with the acute pneumonitis which is the result of local irritation. Although many clinical and experimental observations are consistent with this hypothesis, the fact that the subcutaneous injection of beryllium compounds results in granuloma formation, not only locally[149, 360] but also in the regional lymph nodes,[149] raises the question whether pulmonary granulomata may not be due to the local action of beryllium, despite the contradictory evidence presented.

A variety of hepatic lesions are found in fatal cases of both forms of pulmonary berylliosis. These do not occur with any degree of regularity, nor do they give rise to overt signs of liver disease. In the acute pneumonic type centrilobular necrosis is the principal finding.[94, 400] Hepatic necrosis also occurs in animals after intravenous injections of beryllium compounds.[348] However, the lesions produced tend to be midzonal in location and do not occur when the the beryllium is administered by the respiratory route.[386] It is quite possible, therefore, that the centrilobular necrosis seen in man is due not to the local toxic action of beryllium but rather to the passive congestion and anoxia that occur terminally in acute beryllium pneumonitis.

In the delayed form of chronic beryllium intoxication, small granulomata, similar to those in the lung, are often found scattered throughout the liver.[62, 79, 400] These are indistinguishable from the lesions seen in sarcoidosis and a number of other related diseases.[194] Chronic passive congestion of the liver secondary to cor pulmonale and heart failure is another abnormality found with some frequency. In rare instances the liver may exhibit central and midzonal necrosis,[79] severe parenchymatous degeneration[79] and a diffuse fibrosis.[94] Whether or not these are directly related to the effects of beryllium is not known.

CARBON TETRACHLORIDE

Because of its widespread use as a solvent, fire-extinguisher and antihelminthic carbon tetrachloride has become one-of the most important causes of toxic hepatitis. Poisoning usually follows inhalation of the vapor in a poorly ventilated enclosed space but may also occur after its ingestion, either by accident or during the course of vermifugation. It is not known whether significan absorption takes place through the skin. It has been suggested on the basis of autopsy[36] and experimental[249] evidence that liver injury is more common after ingestion tha after inhalation of carbon tetrachloride However, this has not been borne out in al autopsy studies.[269]

In animals, as little as 0.02 ml. of carbo tetrachloride per Kg. is capable of producin histologically demonstrable hepatic lesions On the basis of some interesting experiment carried out on criminals awaiting execution,[82] it would appear that only slightl larger doses (5 ml.), well within the ant helminthic therapeutic range, occasionall produce similar lesions in man. Althoug these are usually not detectable clinically, must be borne in mind that there are marke individual differences in susceptibility, that even very small doses of carbon tetr chloride may occasionally inflict serious i jury. Fatal intoxication has been reporte after the ingestion of as little as 1.5 ml.[2] yet recovery has followed poisoning wi amounts in excess of 100 ml.[209] With respe to the toxic level of carbon tetrachloride the atmosphere, it is obviously a function n only of the concentration but also of t duration of exposure. On the basis of anim experiments it has been estimated that concentration in excess of 0.01 per cent air is required to produce clinically dete able intoxication in individuals chronica exposed to carbon tetrachloride vapor their work.[370] The time-dose relationsh under other conditions have not been work out.

There is convincing clinical and expe mental evidence to indicate that alcol greatly increases the susceptibility to carb

chloride. In one autopsy series,[269] for
nple, 11 out of 12 fatal cases of acciden-
poisoning occurred in alcoholics. Simi-
, in a group of 34 individuals undergoing
tment for hookworm infestation with
l doses of carbon tetrachloride, the only
stances of toxicity were encountered in
holics.[363] The results of animal experi-
ts confirm these clinical observations.[200]
mechanism underlying this synergism is
known, but it has been suggested that
hol, by virtue of its solvent properties,
enhance the absorption of carbon tetra-
ride from the intestinal tract[200] and fa-
ate its penetration and storage in cells,[331]
hat it may render the liver more suscepti-
to injury by increasing its fat content.[269]
vever, neither of these theories alone ac-
nts for the fact that alcohol enhances the
city of both ingested and inhaled carbon
chloride, that it increases the severity
njury both in the liver and the kidney,
that the increased susceptibility is seen
hronic alcoholics who have not been
king immediately prior to poisoning.[269]
of interest to note, moreover, that while
hol enhances the acute toxic effects of
on tetrachloride, it does not increase the
rity of the hepatic lesions in chronic
oning.[201]

he susceptibility to carbon tetrachloride
appears to depend on the nutritional
us. In animals, at least, it has been shown
inanition[117] and high fat diets[39] increase
toxicity of carbon tetrachloride, while,
risingly enough, low-protein diets do
[38] The importance of these factors in man
not been investigated.

athologic changes in fatal cases of car-
tetrachloride poisoning[269] closely resem-
hose described in experimental animals.[51]
hepatic lesions are characterized by a
ise fatty degeneration and necrosis of the
rilobular parenchyma, collapse of reticu-
, hemorrhage, and leukocytic infiltration.
eneration occurs early and proceeds from
ct cells at the periphery of the lobule. In
nals cytologic changes are evident within
w hours and reach a maximum in 24 to
hours; regeneration is active by the third
and recovery is complete by the four-
th day. Individuals who have succumbed
enal failure as long as 18 days following
intoxication still show signs of liver injury,[269] which suggests that recovery may proceed at a somewhat slower rate in man. Massive hepatic necrosis is rare. It will be recalled that the same is true in animals, unless the carbon tetrachloride is injected directly into the portal vein.[52]

Renal lesions are invariably present in fatal cases and may be the cause of death. The principal findings include degenerative changes in the tubules, the presence of heme and cellular casts, cellular infiltration of the supporting connective tissue, and signs of active regeneration in the tubular epithelium.[269]

The pulmonary findings in carbon tetrachloride are of considerable interest and are seen with great regularity in individuals who survive for longer than 8 days. Characteristically, the alveoli exhibit a fibrinous exudate with pseudomembrane formation, fibroblastic thickening of their walls, and proliferation of their epithelial lining cells.[397] These probably are related to renal insufficiency and are identical with those seen in other forms of acute renal failure. In addition, the lungs frequently show edema, hemorrhage, congestion and bronchopneumonia, features that are thought to be the result of shock, infection and other factors unrelated to the direct effects of carbon tetrachloride. Right-sided dilatation of the heart often accompanies these pulmonary changes.

Areas of atypical focal pancreatitis are also seen.[269] These too are probably related to the kidney damage, since they have been observed in other types of acute renal failure. As a rule, the lesions are limited in extent and severity and do not give rise to overt symptoms.

Clinical manifestations of acute carbon tetrachloride poisoning may be grouped into those related to (1) the general toxic and pharmacologic effects of the agent, (2) liver damage and (3) renal injury. Although any one of these may predominate, careful examination usually discloses evidence of all three. Often the three groups of symptoms overlap, so that it may be impossible to specify their origin.

The general toxic and pharmacologic effects of the poison are the first to become evident. They usually appear within a few hours but may be delayed for as long as a day. With very large oral doses and, even more commonly following inhalation of toxic fumes, the onset may be immediate. The most frequent symptoms during this period include dizziness, headache, nausea and vomiting. In more severe cases, there may be confusion, abdominal cramps, diarrhea, generalized muscle pain and vasomotor collapse. Occasionally, exposure to a high concentration of fumes results in a deep but transient narcosis due to the anesthetic properties of the agent. Death seldom occurs during this initial period. Occasionally, even fatal doses of carbon tetrachloride do not produce immediate symptoms, so that the first signs of intoxication are delayed until hepatic or renal involvement becomes evident some days later.

Clinical signs of liver involvement appear from 2 to 4 days after intoxication, apparently a day or two behind the maximum injury demonstrable histologically. Jaundice and hepatomegaly are the principal clinical manifestations; however, it is evident from autopsy findings[269] that extensive hepatic necrosis may occur without producing either. It is important, therefore, to check the functional status of the liver in evaluating the severity of carbon tetrachloride intoxication. The gastro-intestinal symptoms which appear shortly after exposure usually increase as the signs of liver damage become evident. In general, there is a correlation between the severity of the poisoning and the depth of jaundice. However, death from renal failure may occur with little or no clinical evidence of hepatic injury.[269, 302, 433]

Autopsy studies[269, 362] indicate that the kidneys are involved about as frequently as the liver, and in many cases renal failure dominates the clinical picture. It has been suggested that there may be an inverse relationship between the severity of the lesions in the kidneys and the liver.[269] Of interest is is the fact that most deaths attributable to hepatitis occur during the first week, while those due to renal failure occur in the second and the third weeks.[397] However, as previously indicated, there is usually evidence of injury to both the liver and the kidneys in all cases. Even in instances of mild intoxication, the urine usually contains albumin and casts during the first few days. In more sever cases, oliguria makes its appearance betwee the second and the fourth days and then ma progress to complete anuria. Azotemia i common and occasionally is accompanied b hypertension. During the period of oliguri the specific gravity tends to become fixe at a level of 1.010, and the urine often con tains a significant number of red blood cell and polymorphonuclear leukocytes. In som cases, however, the urine shows very littl other than a reduced volume and a low spe cific gravity, despite the presence of sever azotemia. The close resemblance of the clin cal picture to that in other forms of low nephron nephrosis has been emphasized.[4] However, it should be recognized that deh dration due to fluid losses from the intestin tract often plays an important role in th development of azotemia and must be take into consideration in planning therapy.

Not infrequently peripheral and pulm nary edema supervene as the azotemia pr gresses. While cardiac failure may be respo sible for this complication in some cas faulty regulation of fluid and electroly balance is often the cause. The dyspnea, t cyanosis and the signs of consolidation th appear terminally are usually due to the p monary lesions associated with azoten previously described. Occasionally, ac pulmonary edema is seen immediately f lowing exposure to carbon tetrachloride. T is thought to be the result of the direct i tant effect of the agent on the alveoli.

It is difficult to predict the outcome in a given case of carbon tetrachloride poisoni In general, the outlook is favorable in ca in which the jaundice is mild and the si of renal impairment minimal or absent. H ever, the prognosis should be guarded e in the course of mild hepatitis, since the pearance of renal failure may be delayed a number of days and then terminate fat If the patient survives the first week he is likely to die of hepatic failure. Similarly azotemia is not evident by the end of the week it is unlikely to develop later, so the outlook for recovery is excellent.

If the initial effects of acute carbon te chloride poisoning are survived, the sign hepatitis usually subside in from 2 t weeks, a period slightly longer than

ired for morphologic restitution of the
in experimental animals.[51] Recovery
renal injury is somewhat slower, but in
ier instance are there residuals. Occa-
ally, cirrhosis follows repeated exposure
ubclinical toxic doses of carbon tetra-
ride,[299] as in experimental animals.[51]
clinical picture in such cases does not
r significantly from that seen in other
s of cirrhosis, so that the diagnosis de-
ds almost entirely on the history of ex-
re. Early recognition of this condition is
cially important, since the cirrhotic le-
may be reversible in its early stages if
her exposure to the toxin is prevented.[51]
he general principles of *treatment* are
ined on page 340. As previously men-
ed, there is no evidence to indicate that
lements of protein, methionine or cho-
exert any *therapeutic* effect in the well-
rished individual. However, it is possible
they may be of benefit in malnourished
viduals if given immediately after intoxi-
on.

wide variety of chemically unrelated
tances, including tocopherol,[176] chloro-
ll,[250] glutathione,[46] sodium thiomalate,[46]
um malate,[46] sodium thioglycollate[46] and
um glycocollate,[46] to mention only a few,
known to protect animals against the
c effects of carbon tetrachloride when
n *prophylactically*. However, they have
been tried as therapeutic agents, either
erimentally or clinically, and their action
ot understood.

CHLORINATED NAPHTHALENES AND DIPHENYLS

ecause of their unique physical prop-
s, the chlorinated naphthalenes and di-
nyls make ideal materials for the insu-
n of electrical wire and condensers.
wever, they are such potent hepatotoxins
they are no longer widely used in indus-
The commercial product employed most
uently, and known as Halowax, consists
a mixture of chlorinated naphthalenes,
, at one time, contained carbon tetra-
ride as a solvent. Experimentally, it has
n shown that the toxicity of the naphtha-
s and the diphenyls is related directly to
r degree of chlorination and is enhanced
greatly by the presence of small amounts of carbon tetrachloride and alcohol.[28]

Although the ingestion of these compounds may lead to poisoning,[28] most cases follow inhalation of fumes given off by the molten agent during the soldering of condensers or the coating of wires.[148] The type of hepatitis produced is unusually severe and often terminates fatally in subacute necrosis or postnecrotic cirrhosis.[114, 148, 388] Characteristically, the onset is insidious with the development of general debility, anorexia and nausea and usually follows prolonged exposure to the toxin. Occasionally, it is heralded by the appearance of an acneform rash (chloracne), one of the well-recognized signs of toxicity in handlers of the chlorinated naphthalenes. Jaundice and hepatomegaly appear a week or two later and are then followed by a decrease in the size of the liver, ascites and edema. The disease runs a chronic downhill course and usually terminates in hepatic coma and death within a few months. Occasionally, however, the lesion is more fulminant, and death due to massive necrosis of the liver supervenes within a period of 2 weeks. Severe abdominal pain is a characteristic feature in such cases. Whether this is due to hepatic necrosis or to the associated acute pancreatitis described by several authors[114, 388] is not known. Very few cases of nonfatal hepatitis have been reported, and no follow-up studies are available to indicate whether recovery without residuals is possible. The remarkable toxicity of the chlorinated naphthalenes and diphenyls for the liver has also been observed in animals, who show the same tendency toward massive necrosis seen in man.[28]

In contrast with carbon tetrachloride, the chlorinated naphthalenes do not produce renal lesions in animals.[28] However, nephrosis has been reported as an occasional complication of hepatitis in man.[388]

DDT

In view of the fact that DDT (2,2 bis [*p*-chlorophenyl]-1,1,1-trichlorethane) is capable of producing central necrosis of the liver in animals,[280] it is regarded generally as a potential hepatotoxin in man. However, despite its widespread use as an insecticide, it has rarely been reported as a cause of toxic hepatitis. In one instance, the accidental ingestion of 120 ml. of a 5 per cent solution in kerosene produced hepatomegaly, gastrointestinal bleeding, oliguria, coma and death.[366] Autopsy revealed extensive central necrosis and periportal fatty infiltration of the liver and severe tubular degeneration and necrosis of the kidneys. Since DDT alone does not produce renal damage,[280] it was suggested that the kerosene used as a solvent was an important factor in the pathogenesis of the lesions. In another case, exposure to DDT used as an insecticide produced jaundice in an individual with an underlying cirrhosis.[222] Rarely, DDT serves as a sensitizing agent. In one such case,[170] it produced periarteritis nodosa. At autopsy the liver showed enlargement due to congestion, periportal fatty infiltration and a large thrombosed vein.

MANGANESE

Industrial workers exposed to manganese dioxide dust and fumes are subject to pneumonia[108] and a highly characteristic neurologic disorder that closely resembles the progressive lenticular degeneration of Wilson's disease.[54, 60, 108] Because of the possible relationship of the neurologic changes in Wilson's disease to the associated cirrhosis, it has been suggested that a similar hepatic lesion may be responsible for the neurologic disorder in chronic manganese poisoning.[60] In support of this hypothesis it has been shown that repeated injections of soluble manganese salts produce cirrhosis in animals.[111, 181] However, a complete review of all the reported cases of manganese poisoning in man[108, 403] discloses only a single instance in which a biliary cirrhosis is said to have been demonstrated.[56] It is highly improbable, therefore, that the type of chronic manganese poisoning encountered in industry produces liver injury.

MUSHROOM POISONING (MYCETISMUS)

Some 70 or 80 species of mushrooms are known to be toxic for man, but only one, *Amanita phalloides*, affects the liver. The others produce gastroenteritis, muscarinic effects, acute hemolysis and disorders of the central nervous system. The unusual toxicity of *Amanita phalloides* is attested by the 50 per cent mortality rate which follows it
ingestion.[119]

Types of Toxin. Two types of toxin hav
been isolated from *Amanita phalloides*, phal
lin, a thermolabile glucoside with hemolyti
properties, and amanito-toxin, a thermo
stable agent which characteristically produce
fatty degeneration and necrosis of the liver
the kidneys and the myocardium.[118] Sinc
the former is readily destroyed by cookin
and during digestion, it probably plays littl
role in human poisoning, although its effect
can be easily demonstrated in animals whe
administered by the parenteral route.[1
There is general agreement, therefore, tha
all of the manifestations of *Amanita pha
loides* poisoning are due to amanito-toxin
which has been identified recently as a mi
ture of cyclic polypeptides.[422] Of interest
the fact that phallin and amanito-toxin a
antigenic and capable of producing specif
antibodies in animals.[118] However, the ant
genicity of amanito-toxin is weak, so that
has never been possible to develop a pote
antiserum for use in treatment.

Pathologic Changes. The principal path
logical changes in fatal cases are found
the liver, the kidneys and the central nervo
system.[91, 399] As a rule, the liver is sm
and exhibits massive hepatocellular necros
intralobular hemorrhages and an acute
flammatory exudate. Although the pictu
has been likened to that of idiopathic acu
yellow atrophy, it differs in that the pare
chymal cells are heavily infiltrated with
droplets and do not undergo the same ty
of rapid autolysis seen in the latter. T
kidneys show varying degrees of swelli
degeneration and fatty infiltration of the tu
lar epithelium, and congestion of the glo
eruli. The principal findings in the cen
nervous system include widespread to
swelling of the cerebral ganglion cells, sc
tered small punctate hemorrhages and p
vascular lymphocytic exudates. Not in
quently the myocardium also shows fa
infiltration and degeneration.

Symptoms. Characteristically, the onse
symptoms following the ingestion of *A
nita phalloides* is delayed for a period
6 to 15 hours. In contrast, most other
sonous mushrooms produce symptoms wi
the first few hours. Nausea, vomit

e abdominal cramps and diarrhea ap-
in rapid succession and are usually fol-
d within a period of 24 hours by severe
ration, signs of dehydration and vaso-
r collapse. In severe cases, coma super-
s, and death ensues in 3 to 8 days.
dice usually appears on the third day[399]
s often absent, even in individuals who
ve for several days and then succumb
vere hepatic necrosis.[91] Enlargement and
erness of the liver and splenomegaly are
nstant findings. Signs of renal injury are
ys present. Early in the course, the urine
ains albumin, casts and red blood cells;
, oliguria and azotemia supervene. Clonic
ms and convulsions may develop termi-
. These are generally attributed to the
ral nervous system lesions found post-
tem,[91] but evidence based on dog ex-
nents suggests that severe hypoglycemia
be a factor in some instances.[183] Hemor-
ic phenomena and anemia are far less
mon than hepatorenal and neural symp-
s but do occur occasionally.

ven the most gravely ill patients with
s of severe hepatic and renal injury may
ver,[399] so that it is difficult to predict the
ome in any given case. Nevertheless,
motor collapse, increasing azotemia and
s of central nervous system involvement
lly denote an unfavorable prognosis. The
very period is variable, in some instances
g as short as 10 days, and in others as
as 6 weeks.[399] Few long term follow-up
ies have been carried out, so that it is not
wn whether the recovery from hepatic
ry is usually complete. However, hepatic
sis has been reported as a sequela in
ral instances,[171] so that residual damage
occur more frequently than is generally
gnized.

herapy. Although there is no specific
apy for *Amanita phalloides* poisoning,
eral supportive measures are of the great-
importance in tiding the patient over the
ial critical period of dehydration and vas-
otor collapse, and the subsequent develop-
nt of hepatic and renal failure. These
ude careful regulation of fluid and elec-
yte balance, transfusion of whole blood,
the provision of sufficient parenterally
ninistered glucose to meet the caloric
uirements and to prevent hypoglycemia.
Gastric lavage and saline purges are usually recommended to rid the gastro-intestinal tract of possible remaining traces of mushroom. However, these procedures are of doubtful value, since there is usually such a long interval between the ingestion of mushrooms and the onset of symptoms. However, they may be of value prophylactically in individuals who have partaken of a bad lot of mushrooms, but are not yet ill.

PHOSPHORUS

With the legal prohibition of the use of elemental yellow phosphorus in the manufacture of matches in this country, acute phosphorus poisoning has become relatively rare. Most cases now occur following the ingestion of roach paste[199, 259] or rat poison.[199] In the Orient, where yellow phosphorus matches are still in use, the incidence of poisoning is still high. As might be expected, the victims are often children.

As little as 15 mg. of yellow phosphorus is capable of producing signs of toxicity, and 60 mg. has been known to cause death.[144] Some roach pastes contain more than 1 Gm. per cent of phosphorus,[259] so that the ingestion of as little as 5 Gm. may be fatal. The severity of the poisoning in the average case is well illustrated by the mortality rate of 75 per cent observed in the 16 cases reported from Charity Hospital in New Orleans.[199]

Red phosphorus, another form of the element, is relatively nontoxic apparently because of its insolubility and nonvolatility. Yellow phosphorus is also poorly soluble but is readily dispersed into an aqueous colloidal solution and is volatile.[144]

Although the hepatic manifestations of phosphorus poisoning are of special interest, it should be emphasized that phosphorus is a potent general protoplasmic poison and may be lethal within 10 hours, even before characteristic tissue changes can be demonstrated histologically.[199]

Symptoms. The initial symptoms, including nausea, vomiting, epigastric burning, abdominal pain and diarrhea, usually occur immediately following the ingestion of phosphorus or within a few hours. These are due to the local action of the poison in the gastro-intestinal tract. However, when the appearance of symptoms is delayed for hours, or even days, it must be assumed that they are related to the systemic effects of absorbed phosphorus. Shortly after the ingestion of phosphorus the breath has a garlic-like odor, and the feces are luminescent in the dark, features that may be of great diagnostic importance.

In severe poisoning, shock and coma follow the initial symptoms in rapid succession, and death may ensue within 48 hours. More commonly, however, the systemic effects become evident from 1 to 3 days after the ingestion of phosphorus, and death occurs during the first week. Although it is highly probable that no tissue is wholly exempt, the liver and the kidneys suffer the most severe injury and manifest the most striking structural and functional changes. As in the case of other severe intoxications, tissue damage is so widespread that it is often difficult to determine the site of origin of any given symptom.

The manifestations of systemic intoxication include intractable vomiting, often with blood-streaked material, diarrhea, abdominal cramps and severe prostration. Signs of severe liver injury can always be demonstrated, although hepatomegaly and jaundice may not develop. Jaundice seldom appears before the fourth day and may be delayed for over a week. The prognosis is somewhat better when jaundice appears late. As in other forms of severe hepatitis, the urine contains bile, and the feces tend to become pale, indicating a suppression of bile secretion. Not infrequently, hemorrhages occur into the skin and the mucous membranes, presumably due to the associated fall in the prothrombin and the fibrinogen levels of the plasma. Other features of severe hepatic failure seen occasionally include edema, hypoglycemia, tyrosinuria and an increase in serum amino nitrogen. Usually the kidneys are affected equally severely. Oliguria and azotemia are common, and the urine usually contains albumin, casts and red blood cells.

The latter part of the course is characterized by coma, delirium and vasomotor collapse and, as indicated previously, is followed by death toward the end of the first week.

Occasionally, even severely poisoned individuals appear to recover completely. How ever, one such case, followed by serial biop sies of the liver over a period of 3 months showed evidence of incomplete healing an progressive fibrosis, a lesion similar to tha seen in animals with chronic phosphorus poi soning.[241] How often this type of postnecroti fibrosis and cirrhosis follows acute phos phorus poisoning in man is not known.

Pathology. At autopsy the liver usually enlarged and exhibits an extensive fatty de generation of the parenchymal cells, which most marked in the periportal areas. Occa sionally, there is also a mild inflammator reaction in the portal triads. Massive necrosi of the parenchyma is said to occur[222] but exceedingly rare. The lesion in experimenta phosphorus poisoning[241] is very similar, bu cellular necrosis is a more prominent featur The renal tubules and the myocardium als show fatty degenerative changes.

Treatment. Gastric lavage with a dilu solution of copper sulfate (0.25 Gm. in glass of water) and a magnesium sulfa purge are usually recommended to rid t intestinal tract of any remaining traces phosphorus. Unfortunately, these are effe tive only if given within the first few hour

Treatment is largely supportive, as ou lined previously. Choline hastens the remov of fat from the liver in phosphorus poiso ing.[33] However, its therapeutic value wou appear to be negligible, since it does n prevent hepatic injury. Moreover, the fat the liver is symptomatic of a serious prot plasmic disturbance and not its cause, that its removal would appear to be relativ unimportant.

SELENIUM

Livestock in areas where the seleniu content of the soil is high develop chronic illness known as "alkali diseas which is characterized by emaciation, loss hair, lameness and sloughing of the hoofs. At autopsy, the principal findings are cirr sis of the liver and myocarditis. Glomeru nephritis, adrenal hemorrhages, erosion the joint surfaces and ulceration of the testinal tract are also seen in some instanc It is now well known that the disease is to the ingestion of selenium-containing gr forage or vegetation, and that it can be rep

d in experimental animals by adding se-
um salts to the diet. A more acute form
oisoning, known as the "blind staggers,"
een in animals whose feed is unusually
in selenium content. In this disease,
ocarditis, ulceration of the intestine and
sion of the long bones are the principal
ings. The liver is usually congested and
ws focal areas of necrosis, but frank cir-
sis is rare. In some strains of rats, the
onic ingestion of seleniferous grain pro-
es not only hepatic necrosis and fibrosis
also adenomas and low-grade carcino-
s.[281]

Himsworth[171] has emphasized the simi-
ty between the hepatic lesions in chronic
nium poisoning and those of experi-
ntal dietetic massive necrosis and has
gested that the former may be the con-
uence of an induced deficiency of sulfur-
taining amino acids related to the replace-
nt of sulfur by selenium in plant protein.
e protective action of casein and methio-
e in animals fed selenium would appear to
port this hypothesis. However, the fact
t cystine does not prevent liver damage
such experiments casts doubt on this in-
pretation.

Of special interest to the clinician is the
estion of whether the ingestion of selenif-
us grain leads to hepatic damage in man.
lividuals living in seleniferous areas have
en shown to excrete appreciable amounts
selenium in the urine, indicating that sig-
cant exposure has occurred. However, to
e none of these has shown evidence of
patic or other disease.[365]

SENECIO

Several species of weed belonging to the
ecio group, and known as ragwort or
nking Willie, produce a peculiar type
liver disease that presents many of the
nical and pathologic features of Chiari's
ndrome. The disease is seen most
quently in horses and cattle raised in South
rica, New Zealand and Nova Scotia. How-
er, it occasionally affects humans who
ve eaten bread made of imperfectly win-
wed wheat contaminated with the seeds of
necio ilicifolius and *Senecio burchelli.* All
e cases recognized thus far have been re-
rted from South Africa, where the disease
occurs principally among poorly nourished white Europeans.[351, 429] This may be related to the experimental observation that protein-deficient diets enhance the toxicity of the senecio alkaloid.[351] Of interest is a very similar disease that occurs in animals exposed to *Crotalaria spectabilis,* a legume used to enrich the soil in some areas.[310] The alkaloids derived both from this plant and senecio owe their toxicity to the same alkanolamine, known as retronecine.

Pathologic Findings. The principal pathologic findings in fatal cases include enlargement of the liver, widespread fibrous occlusion of the hepatic and the sublobular veins, and intense congestion and destruction of the centrilobular parenchyma. The stroma usually is uninvolved, and there is little or no significant inflammatory reaction. Occasionally, organizing thrombi can be demonstrated in the larger hepatic veins. In more chronic cases there is, in addition, fibrosis and round-cell infiltration of the portal zones, giving rise to the picture of cirrhosis.[351, 429] There is general agreement that the primary lesion is in the vessels, and that the parenchymal changes are secondary to intense congestion. However, it is not known whether the fibrous occlusion of the central and the sublobular veins follows a proliferative endophlebitis or is the end result of thrombosis and organization. Somewhat similar lesions are seen in animals following experimental senecio poisoning, but cirrhosis is more common, and the capillaries appear to be involved more seriously than the veins.[330, 429]

Clinical Features. The clinical features are highly characteristic.[351, 429] There is usually a sudden onset of gnawing and colicky epigastric pain, followed within a few days by a rapidly developing ascites. The liver enlarges and within a few weeks becomes firm. Jaundice is an inconstant finding and, in one series[351] at least, occurred in only 2 out of 12 cases. Vomiting and diarrhea are present in about a third of the cases. Splenomegaly appears to be unusual, despite the obvious development of portal hypertension. Low-grade fever is seen occasionally late in the disease. In severe intoxication there may be early vasomotor collapse, followed later by hematemesis and melena.

The clinical course is usually prolonged and is characterized by rapid reaccumulation of ascites, necessitating frequent paracenteses, recurrent attacks of abdominal pain, and cachexia. Hypoproteinemia is common, but edema is an inconstant finding. Death occurs in approximately half the cases within a period of 1 to 3 months. Despite the apparent progressive downhill course in the remaining patients, clinical recovery ultimately takes place over a period of several months up to 2 years. Whether or not the recovery is complete in such cases is not known, since no long-term follow-up studies have been carried out.

It is highly probable that mild cases of intoxication occur, but these have not been described in the literature.

Treatment. No specific therapy is available in this disease, so that treatment is entirely supportive.

TETRACHLORETHANE

Of all the chlorinated hydrocarbons, tetrachlorethane is by far the most toxic. During World War I it was used widely as a solvent for cellulose acetate, chiefly in the "dope" used in varnishing the canvas surfaces of airplanes and, to a lesser extent, in the manufacture of rayon and lacquers. However, it proved to be so toxic that it was abandoned as soon as a suitable substitute (amyl acetate) could be found. During World War II it became necessary to revive its use, since it was found to be the only satisfactory solvent for impregnating clothing with materials capable of neutralizing poisonous gases.[151] Despite the imposition of stringent engineering and hygienic controls, signs of toxicity were encountered once again in a high proportion of workers exposed to the agent. However, the control measures were successful in preventing serious intoxication, so that no fatalities resulted.[150]

Intoxication usually follows inhalation of the agent but may occur also following its absorption from the skin or the intestinal tract. For reasons that are not entirely clear, females are more susceptible than males, and in both sexes intoxication is more common after the age of 30.[151] The toxic level of tetrachlorethane in the atmosphere has been estimated to be something in excess of 10 parts per million for individuals exposed fo long periods. The odor, which closely resem bles that of carbon tetrachloride, is readil detectable at a concentration of 25 parts pe million.[150]

Pathologic Findings. The principal patho logic finding in fatal cases is a subacute o massive hepatic necrosis with preservatio of the stroma, marked fatty infiltration o surviving parenchymal cells, absence o hepatocellular regeneration, and active pro liferation of bile ducts.[374] The early lesion in non-fatal cases have not been described Fatty degenerative changes are also seen i the renal tubules and myocardium. Essen tially the same lesions have been observe in rats exposed to tetrachlorethane vapor.[37- 424]

Symptoms. The early symptoms of tetra chlorethane intoxication are of two type gastro-intestinal and neurologic.[150] Follow ing exposure to low concentrations of th vapor for a number of weeks, there is a insidious onset of anorexia, nausea and vom iting, or of headache, giddiness, drowsine and paresthesias. These may occur singly in combination and often are associated wit hepatomegaly and impairment of liver fun tion. Jaundice is also present in approx mately 10 per cent of such individuals. O casionally, jaundice appears before th development of other symptoms. Prom cessation of exposure to the contaminat environment at this stage results in rap recovery, usually within a period of less th a month. Of possible diagnostic significan in early toxicity is the tendency for the a solute and relative number of large mon cytes in the peripheral blood to increase.

In more heavily exposed individuals, t onset is similarly delayed and gradual, b gastro-intestinal symptoms, hepatomega and jaundice are constant findings and us ally are associated with tenderness of t liver and weight loss. Not infrequently t jaundice is intense and persists for wee and even months following the last exposu to tetrachlorethane. Recovery is still pos ble at this stage,[267] but some individuals r a progressive downhill course, develop cites and die of hepatic failure.[424] These a the cases that, at autopsy, show subac hepatic necrosis and postnecrotic scarring.

efore the toxicity of tetrachlorethane was understood and appropriate protective sures instituted, the exposure tended to eavy and often was continued long after s of intoxication had appeared. As a re- the hepatitis produced was of unusual rity. In one such series of 70 cases, for mple, the mortality rate was 17 per .[207] In contrast, no fatalities were seen more recently studied group of 55 cases ountered in a carefully supervised plant. reover, the disease was so mild that only f the 55 developed jaundice.[150]

TOLUENE

oluene, one of the aromatic hydrocar- s derived from coal tar, is widely used ndustry, especially in the manufacture of ts and lacquers. Although it shares the ellent solvent properties of its homologue zene, it is far less toxic. In individuals osed to the high concentration usually ountered during spray painting, toluene ears to exert no significant ill-effects. patomegaly and mild macrocytic anemia relatively frequent findings, but no in- nces of frank toxic hepatitis or aplastic mia have been reported.[147] The nature of hepatic enlargement has not been inves- ted. However, animals exposed to similar centrations of toluol show mild degenera- changes in both the liver and the neys.[369]

TRINITROTOLUENE (TNT)

Munition workers exposed to TNT are ject to a number of toxic manifestations which hepatitis and aplastic anemia are most important.[227, 246, 291] Functional dis- bances of the gastro-intestinal, the circula- y and the central nervous systems, and al irritation of the respiratory tract and skin are often troublesome but rarely give to serious difficulty. Absorption is chiefly m the skin and, to a lesser extent, from mucous membranes.[15, 207] The presence the skin of oil and grease, in which TNT soluble, enhances absorption and increases chances of intoxication.[15, 270] It is gen- ally stated that inhalation of the fumes is thout danger,[270] but this view is not shared all investigators.[246]

Clinical Features. The hepatitis produced by TNT has a great many unusual features, very few of which have been adequately explained. Among these may be mentioned the following: (1) Only a small proportion of individuals exposed to TNT develop hepatitis.[246] (2) Signs of hepatic damage usually appear only after many weeks of exposure,[246] or, in some instances, not until several months after cessation of exposure.[425] (3) The disease is almost always severe, being characterized by a prolonged course and a high fatality rate. (4) Massive and subacute necrosis of the liver occur far more frequently and resemble the lesions of idiopathic acute yellow atrophy far more closely than almost any other known type of toxic hepatitis.[173, 383, 384] (5) Considerable difficulty has been encountered in reproducing the lesion in animals,[171] an unusual circumstance for an agent presumed to be a true hepatotoxin.

In many respects these unusual features are reminiscent of the hypersensitivity type of hepatitis produced by drugs like cinchophen. However, the chemical structure of TNT and its failure to produce other manifestations of hypersensitivity make it highly improbable that it is a sensitizing agent. Himsworth[171] has suggested that the long latent period, the occurrence of massive hepatic necrosis, and the failure to reproduce the lesion in animals on normal diets may indicate that TNT injures the liver indirectly by inducing a relative deficiency of sulfur-containing amino acids. In support of this hypothesis, he has pointed out that TNT raises the metabolic rate and thus increases the demand for protein, that at least 2 of its 3 isomers combine with amino acids and make them unavailable, and that by reducing the protein content of the diet it is possible to reproduce TNT hepatitis in experimental animals. However, it should be noted that the isomer of TNT which does not combine with amino acids also produces toxic hepatitis, and that a low-protein intake favors the development of hepatic necrosis in experimental animals only when the diet is high in fat. The question may be raised, therefore, whether the peculiarities of TNT toxicity may not be related to its solubility in fat. It is possible that dietary fat enhances the absorption of TNT from the intestinal tract and favors its retention in the liver at high concentrations by producing fatty infiltration. Similarly, the enhanced absorption of TNT from the skin in the presence of grease[15, 270] may account for the sporadic occurrence of intoxication in groups of apparently equally exposed individuals. As for the long latent period, it does not necessarily point to an induced nutritional deficiency, as previously indicated, but may reflect a slow cumulative intoxication with an agent which is absorbed relatively slowly. In cases where the signs of liver disease appear weeks or months after the last exposure to TNT, it is possible that the initial injury incurred during exposure is asymptomatic, and that the lesion produced is progressive.

Symptoms. The onset of symptoms is usually insidious, with anorexia, nausea and vomiting. Jaundice appears within 2 weeks and usually is followed by hepatomegaly. In severe cases, abdominal pain is a prominent feature, and the liver may be small. The course is usually prolonged and often complicated by the development of ascites and hemorrhagic phenomena. Occasionally, there is an associated disturbance of the hemopoietic system, as evidenced by severe leukopenia,[383] macrocytic anemia[383] or aplastic anemia.[291] Both hyperplastic[383] and aplastic[246] bone marrows have been described, suggesting that the changes in the peripheral blood may be due to a maturation arrest in some cases.

Prognosis. The outcome is unpredictable. Most of the cases reported in the literature have either died within a few weeks of acute massive necrosis of the liver[173, 246] or run a chronic progressive downhill course, succumbing ultimately to hepatic failure as a result of postnecrotic cirrhosis.[384, 425] However, it is known that many individuals with TNT hepatitis recover. Unfortunately, little is known about the nature of the lesion in this group or its ultimate fate. In one 3-year follow-up study of 17 such cases,[384] there were no clinical residuals, suggesting that the initial lesion may have been zonal rather than massive. However, reports of postnecrotic cirrhosis becoming evident as long as 10 years after apparent recovery from TNT hepatitis[173, 425] illustrate the fact that the scarred postnecrotic liver may be difficult to recognize clinically and may decompensate unexpectedly years after its inception It is highly probable that such lesions can be recognized much earlier by the use of sensi tive tests of hepatic function and especially by needle biopsy of the liver.

Treatment. Methionine supplements and diets rich in protein and vitamins have been recommended as a specific form of therapy in TNT hepatitis.[97] However, the beneficia results reported are not convincing, especially since no control studies have been carried out.

ANESTHETIC AGENTS

In evaluating the role of an anesthetic agent in the pathogenesis of postoperative hepatitis, due consideration must be given t the nature of the underlying disease, the de gree of anoxia attained during anesthesia an the presence of such complicating factors a shock and infection, since each of these alon is capable of producing liver injury.

CHLOROFORM

Chloroform has the well-deserved reputa tion of being a dangerous hepatotoxin. A though it has been largely supplanted b other less toxic anesthetic agents, it is sti used to some extent in various parts of th world for obstetric and minor surgical pr cedures. Most fatalities have followed pr longed anesthesia, especially during partur tion, but deaths have occurred also after little as one half ounce of chloroform. Women undergoing prolonged labor appe to be peculiarly susceptible to this type anesthetic death. This has been ascrib to the malnutrition and infection which frequently accompany such labors,[335] hypothesis consistent with the experime tal observation in animals that malnut tion[143, 266] and infection[285] enhance the hep totoxic effects of chloroform.

From the paucity of reports dealing w non-fatal cases of chloroform hepatitis, it easy to gain the erroneous impression th chloroform either injures the liver seriou or not at all. However, it has been sho in animals that even a 30-minute period chloroform anesthesia causes significant i pairment of hepatic function, which may p sist for as long as eight days.[332]

Clinical Features. The clinical manifes s of severe chloroform intoxication follow niform pattern.[132, 335, 376] Characteristi- y, the onset of symptoms is delayed for o 72 hours following recovery from anes- ia. Drowsiness and vomiting then make r appearance and are soon followed by ndice. The vomiting is usually copious often becomes coffee-ground in nature. the fourth day the drowsiness usually has pened to the point of coma, and in ap- ximately half the cases is followed by vulsions. Despite the regular occurrence severe hepatic damage, some cases fail to elop jaundice,[376] a phenomenon difficult explain on the basis of our current concept pigment metabolism. Fever is unusual, ept terminally. Azotemia and acidosis ur early and tend to increase in severity. hough these are usually associated with uria and albuminuria, in occasional cases urinary volume and the urea content are h,[132] suggesting that the azotemia may be ated in part to the rapid breakdown of tein, rather than to renal failure and ydration alone.

Most severely intoxicated individuals die 3 to 8 days, but an occasional case sur- es and goes on to complete recovery. siduals are unlikely in such cases, since the aracteristic lesions seen at autopsy are hal in type. Complete recovery without rring also occurs in animals exposed to nfatal doses of chloroform.[419] Individuals o are exposed to repeated doses of chloro- m at frequent intervals occasionally de- lop a progressive cirrhosis. In one such se described by Wilcox,[424] small amounts chloroform were inhaled daily over a riod of 6 months, at the end of which time ndice and hepatomegaly developed. Sub- quently, ascites and other signs of cirrhosis peared, and death ensued in 18 months.

Pathology. At autopsy the liver is usually normal size but may be small. Hepato- llular necrosis is invariably centrilobular distribution and never massive, as in acute llow atrophy. Varying fractions of the bule are destroyed, but a small rim of intact lls is always present around the portal ads. The necrotic cells break up into hy- inized fragments and undergo lysis, while e intact cells peripherally show marked tty infiltration. As in other types of toxic patitis, the reticulum is not destroyed and usually is infiltrated with a number of phagocytic mononuclear cells at the sites of necrosis. The remaining hepatic cells show little evidence of regeneration. Almost identical hepatic lesions have been described in the dog.[419] The changes in the kidney are less conspicuous than in carbon tetrachloride poisoning and usually consist of fatty infiltration of the convoluted tubules.

During the past decade considerable attention has been directed to the interrelationships between the hepatotoxic effects of chloroform and certain dietary factors. In brief, it has been shown that starvation,[143] protein-depletion[266] and a high fat intake[286] increase the susceptibility to hepatic damage by chloroform, and that diets rich in protein[143] and carbohydrate[143] are protective when given *prophylactically*. Moreover, it has been found that protein, methionine and, to a lesser extent, cystine protect *protein-depleted* animals against chloroform toxicity if given from 24 hours before to as late as 4 hours after anesthesia.[265, 266] The theoretical implications of these observations have been discussed elsewhere (p. 332). The point that should be emphasized here is that none of these experimental observations is concerned with the *therapeutic* effects of these supplements when administered *following* the development of toxic hepatitis, so that they do not provide the sound basis for treatment that is needed.

DIVINYL ETHER

Because divinyl ether is capable of producing centrilobular necrosis in dogs,[141] it is generally regarded as a potential hepatotoxin in man. In the dog, there is a close correlation between the severity of the hepatic damage produced and the duration of anesthesia, the nutritional status and the degree of oxygenation.[141, 142] For that reason, certain precautions have been recommended. These include administration of carbohydrate preoperatively, limitation of the duration of anesthesia to 1 hour, use of oxygen whenever the period of anesthesia is to exceed one half hour, and avoidance of divinyl ether in patients with liver disease.[311] Under these conditions, no instances of hepatic injury have been encountered in an extensive clinical experience with this agent.[311] Although it would be unwise to abandon this cautious attitude toward divinyl ether, it should be recognized that its hepatotoxicity for man has not been proved, and that the human liver may be as resistant to it as the monkey's.[141]

ETHER (DIETHYL ETHER)

There are no clinical reports of toxic hepatitis following ether anesthesia. However, there is experimental evidence to indicate that, in the dog at least, ether is capable of producing mild liver injury[142] and transient impairment of hepatic function.[332] Bromsulphalein retention has also been reported following ether anesthesia in man,[68] but these observations are difficult to interpret in terms of toxicity, since circulatory disturbances and alterations in hepatic structure incidental to surgical manipulation may also affect dye clearance.

TRIBROMETHANOL (AVERTIN)

As a member of the halogenated hydrocarbon group, Avertin might be expected to behave as a potent hepatotoxin. Actually, however, it produces only slight liver damage in dogs[41] and never has been implicated as a cause of toxic hepatitis in man. Nevertheless, it is generally assumed that the presence of liver disease contraindicates its use as an anesthetic agent, since the bromsulphalein retention that usually follows Avertin anesthesia, both in man[68] and in experimental animals,[41] is significantly enhanced in the presence of hepatic damage. A more urgent reason for exercising caution in the patient with liver disease is the danger of delayed recovery from anesthesia related to a decrease in the rate of Avertin detoxification.[41]

ANTIARTHRITIC AGENTS

CINCHOPHEN

Hepatitis is by far the most serious complication of cinchophen therapy and is largely responsible for the decline in the use of this agent over the past 2 decades. Although it occurs infrequently, probably in less than 0.1 per cent of patients under treatment,[371] it has a mortality rate close to 50 per cent.[288] This has encouraged a search for less toxic derivatives of cinchophen, but these have proved to be no safer than the parent substance. Included in this group are neocinchophen (the ethyl ester of methyl cinchophen farastan (mono-iodo-cinchophen), biloptin (di-iodo-cinchophen), oxiliodide (cinchophen hydroiodide), and guphen (the guaiacol ester of cinchophen).

Clinical Features. A number of feature strongly suggest that the hepatitis produce by cinchophen is a manifestation of dru hypersensitivity. These include the following (1) The hepatitis frequently is associate with other symptoms suggestive of an allergi reaction, such as pruritus, rash, fever arthralgia and edema.[307, 358] (2) The ingestion of cinchophen sometimes is followed b sudden vasomotor collapse, respiratory distress and syncope, a syndrome closely resembling an anaphylactic reaction.[17, 307, 358] (3 There is usually a long latent period betwee the onset of drug therapy and the appearance of symptoms.[25, 415] (4) The reaction are particularly likely to occur in individua previously exposed to the drug.[76] (5) Neith the incidence nor the severity of the hepatit can be correlated with the amount of cinchophen ingested. (6) There is a remarkab tendency for the lesion to progress aft withdrawal of the drug.[288] (7) Even leth doses of cinchophen fail to produce signi cant hepatic lesions in experimental an mals.[179, 208, 314] Skin tests for hypersensitivi are positive only occasionally,[312, 358] and t results of attempted passive transfer of an body by the Prausnitz-Küstner technic a of precipitin tests are uniformly neg tive.[307, 358] However, as previously indicate these are seldom positive in other types drug hypersensitivity.

Hepatitis usually appears during pr longed cinchophen therapy, often weeks months after its institution. In occasion instances, however, signs of liver damage not become evident for as long as 6 mon following cessation of drug ingestion.[288] It this long period of latency and the frequ occurrence of massive hepatic necrosis th have led to the suggestion that the injury the liver may be based on an induced nut tional deficiency.[173] There is no clinical e dence to support this hypothesis, and, inde it has been shown that the restriction of p tein and methionine in the diet does not ov come the natural resistance of animals

atic injury by cinchophen.[179] Other pos-
e interpretations of the significance of
longed latency have been discussed else-
ere (p. 338).

Attempts have been made to correlate the
elopment of cinchophen hepatitis with
presence of antecedent liver disease[221] or
pairment of hepatic function,[221, 312] on the
ory that they may render the liver more
ceptible to injury, or lead to the occur-
ce of abnormal toxic metabolites. How-
r, in animals, previous damage with toxic
nts, such as chloroform and phosphorus,
s not sensitize or predispose the liver to
ury by cinchophen,[208, 314] and as yet no
ic metabolites of cinchophen have been
lated.

Postmortem Findings. The high mortal-
rate in this form of hepatitis is related
the frequent development of acute and
acute massive necrosis of the liver. Al-
st invariably postmortem examination
eals a small liver without significant
dulation, even when the patient has sur-
ed for a number of months.[25, 212, 228,
313] This is merely a reflection of the fact
t the destruction is usually extensive, and
t there is little evidence of hepatocellular
generation. Most of the parenchymal cells
ve either undergone lysis or show severe
generative changes, including fatty infiltra-
n, vacuolization and hyaline necrosis. The
lammatory reaction is variable, being
nimal in some cases and intense in others.
in other types of acute massive hepatic
crosis, there is collapse and condensation
the reticulum framework and active regen-
ation of bile ducts, but no fibrosis. In older
ions, however, the areas of collapse are
ten the site of connective tissue prolifera-
n. Superficially at least, the gross and the
icroscopic pictures resemble those of idio-
thic acute yellow atrophy. However, the
sence of regeneration or any tendency
ward a zonal pattern of necrosis, and the
esence of widespread degenerative changes
the remaining cells serve to distinguish the
o. Except for the frequent occurrence of
generative changes in the epithelium of the
nal tubules, and certain alterations to be
pected as secondary manifestations of se-
re hepatic failure, there are no other
orphologic signs of cinchophen toxicity.

The nature of the hepatic lesions in nonfatal cases is not known, but there is no reason to believe that it differs fundamentally from that seen at autopsy, except possibly in extent. This raises the question of whether or not restoration of the normal architecture is possible following recovery. Of 3 such cases studied at the Mayo Clinic, 1 exhibited a nodular liver at operation, and 2 had relapses subsequently that proved to be fatal.[415] It is quite possible, therefore, that postnecrotic scarring is more frequent than is generally recognized. This might be anticipated from the nonzonal nature of the necrosis seen in fatal cases.

Symptoms. The onset of symptoms is usually sudden, with anorexia, nausea and vomiting. These may be accompanied by chills and fever, pruritus or urticaria. Jaundice usually follows within a few days but may be delayed for weeks or even months.[415] A few instances of anicteric hepatitis have been described,[307, 415] but these are rare. The jaundice increases in intensity, usually reaching its maximum in a few days and then persists. As might be expected from the nature of the hepatic lesion, bilirubinuria and pale or clay-colored stools are seen early. Albuminuria, cylindruria and oliguria are common, but severe renal failure is rare. The subsequent course is variable.[415] In fulminant cases, the patient lapses into coma and dies of hepatic failure within the first few weeks. This is by far the most common type of death. Other cases run a chronic course, occasionally interrupted by clinical remissions, ultimately develop ascites and edema and die within 6 months of hepatic failure or bleeding from esophageal varices. The most favorable cases improve slowly and go on to apparent recovery in 6 to 8 weeks. As previously indicated, the prognosis in this group must be guarded, since relapse and evidence of progression may appear at a later date. Of interest in this connection is a recent report[34] of cholangiolitic cirrhosis with xanthomatosis, presumably due to intrahepatic biliary obstruction, which appeared 18 years following neocinchophen therapy. There was no immediate reaction to the drug, but it was considered possible that an anicteric hepatitis had occurred and then progressed at a subclinical level for a number of years. This is a reasonable interpretation, in the light of experience with other drug reactions, although it is difficult to exclude alternative possibilities.

GOLD

The gold compounds used in the treatment of rheumatoid arthritis and lupus erythematosus frequently produce manifestations of toxicity. These fall into two groups: (1) anaphylactoid and febrile responses immediately following an injection and (2) delayed reactions involving the skin, the mucous membranes, the gastro-intestinal tract, the liver, the kidneys and the hemopoietic system.[8, 70] It is not known whether these are due to drug intoxication or to sensitization, but the latter is generally considered more likely.

Hepatitis is one of the less common complications of gold therapy and is said to be clinically indistinguishable from the viral type.[162] Since many of the cases reported have occurred in individuals undergoing group therapy in large outpatient clinics,[162] it is quite possible that they represent instances of syringe-transmitted viral hepatitis. Unfortunately, no epidemiologic or histologic data are available to substantiate this possibility. Acute yellow atrophy is also said to occur rarely,[90] but in none of the cases reported has the diagnosis been established by postmortem examination. In the few fatalities that have been investigated,[8] the changes in the liver have been of a nonspecific nature, and no lesions suggestive of a hypersensitivity reaction have been described.

BAL has proved to be of some value in the treatment of dermal reactions following gold therapy.[244] Although it is worth a trial in all cases, it is not known whether it has any effect on the course of more serious reactions involving the liver, the kidney and the hemopoietic system.

PHENYLBUTAZONE (BUTAZOLIDIN)

The high incidence of untoward reactions to phenylbutazone is a limiting factor in its usefulness as an antiarthritic agent.[379, 381] Many of these, including rash, fever, agranulocytosis, thrombocytopenia, lymphadenopathy and swelling of the salivary glands, appear to be manifestations of drug hypersensitivity. However, others, such as edema and peptic ulcer,[197, 357] are probably based on other mechanisms. Hepatitis, one of the rare complications of phenylbutazone therapy,[378, 379, 385] has been associated almost invariably with agranulocytosis, so that it too is probably a manifestation of drug sensitization. In the only fatal case reported,[378] perivascular inflammatory lesions and granulomata typical of sensitization reactions were demonstrated in the heart and the lungs, but, oddly enough, the liver showed no significant changes other than congestion, despite the fact that deep jaundice had been present for 3 days. Since there was nothing to suggest a hemolytic reaction, and since the urine contained both bile and increased amounts of urobilinogen, it must be assumed that hepatocellular injury was present, although not detectable histologically. It is noteworthy that phenylbutazone hepatitis can occur also in the absence of jaundice. In one such case[38 the liver became significantly enlarged and tender, and there was a concomitant increas in bromsulphalein retention.

ANTIBIOTICS

Some of the antibiotics are capable of injuring the liver, either directly by a toxi action or indirectly by inducing a hypersensitivity reaction. However, many of th infections for which they are used also produce hepatitis, so that it is often difficult t evaluate the role of antibiotics when th complication occurs. Moreover, in patien undergoing prolonged therapy the possibilit of syringe-transmitted viral hepatitis must b considered. Recently, it has also become apparent that broad-spectrum antibiotics fav the development of disseminated mycotic infections and the emergence of resista strains of staphylococci, both of which ma produce an acute suppurative focal hepatiti

CHLORAMPHENICOL (CHLOROMYCETIN)

A small proportion of individuals on chlo amphenicol therapy develop severe blo dyscrasias related to depression of the bo marrow.[161, 218] Such reactions are thought be due to drug hypersensitivity, althou other possibilities have not yet been exclude In at least 2 instances, jaundice has be reported as a complication. In one of these, the jaundice appeared after the developme of aplastic anemia and was due to an infe tion of the liver with staphylococci and ca

a, so that the drug was implicated only
y indirectly. In the other,[161] an individual
h a history of penicillin sensitivity in the
st, nausea, vomiting and vertigo developed
mediately following a second course of
loramphenicol. Jaundice appeared on the
rd day and then cleared promptly. Signs
aplastic anemia did not become evident
r 2 months. At autopsy 2 weeks later the
er was normal. Possibly the jaundice in
s case was the result of a hypersensitivity
action involving the liver. This would be
nsistent with the observation that chloram-
enicol does not injure the liver in ani-
als[367] or in patients with hepatitis.[158] Rou-
e biopsies in individuals without hepatic
sease also have failed to demonstrate
anges in the liver following chlorampheni-
l therapy.[437]

CHLORTETRACYCLINE (AUREOMYCIN)

Therapeutic doses of *orally* administered
lortetracycline frequently produce a fine
tty vacuolization of the hepatic parenchyma
at is readily reversible on stopping the
ug.[339, 341, 437] However, the drug appears to
ve little effect on hepatic function, even in
tients with antecedent liver disease,[67, 353]
that the lesion probably has no clinical
portance. *Intravenous* chlortetracycline, on
e other hand, is capable of producing sig-
ficant liver damage, as evidenced by im-
irment of function, clinical jaundice and
epatomegaly.[19, 214, 338] This is likely to oc-
r particularly in individuals who have re-
ived excessively large doses intravenously
addition to oral medication,[19, 214] but sig-
ficant injury has been observed also after as
tle as 1 Gm. intravenously for 3 days.[338]
bviously, there is the possibility that the
epatitis in such cases is due to the asso-
ated infection. However, the same type of
jury has been produced experimentally
oth in man[19] and in animals,[215] so that
ere is little reason to doubt that intrave-
ous chlortetracycline is potentially hepato-
xic. Histologically, the liver shows the same
pe of fine fatty vacuolization seen after the
ral administration of chlortetracycline, but
e centrilobular cells tend to undergo au-
lysis and fragmentation, and bile thrombi
re common.[19, 214] In animals, it has been
ound that inactivation of chlortetracycline
y heat does not abolish its toxicity for the
liver, suggesting that the hepatic lesions are due to a direct chemical effect and not to an indirect action related to chlortetracycline's antibiotic activity.

Of special interest is the observation that chlortetracycline protects animals against the massive hepatic necrosis produced by low-sulfhydryl, low-tocopherol diets, an effect thought to be related to inhibition of the intestinal flora and a reduction in the formation of hypothetical hepatotoxic bacterial metabolites.[155] On the principle that similar bacterial factors may be of importance in the pathogenesis of hepatic coma, chlortetracycline has been recommended as a therapeutic agent in that condition.[110] On the whole, the results of this form of treatment have been very disappointing, except in rare instances of hepatic coma due to acute viral hepatitis.

Large doses of chlortetracycline also protect against the hepatic and the renal effects of choline deficiency in rats.[21] The mechanism of this action is not known, but appears to be related to the antibacterial properties of the drug.

OXYTETRACYCLINE (TERRAMYCIN)

Fine fatty vacuolization of the hepatic parenchyma occurs with great regularity following therapeutic doses of oxytetracycline given either orally or parenterally over a period of several days.[190, 341] The lesion appears to have no clinical significance, since it is readily reversible following withdrawal of the drug and gives rise to neither symptoms nor significant impairment of hepatic function, even in patients with pre-existent liver disease.[190] Similar lesions have been observed in mice and dogs,[215] but not in rats.[182] It is not known whether the effect of oxytetracycline on the liver is related to a direct toxic action or to the development of an induced choline deficiency.

Severe reactions resembling serum sickness are known to occur in individuals receiving oxytetracycline,[186] so that the occasional development of drug hypersensitivity hepatitis is to be anticipated. However, no such cases have as yet been reported.

PENICILLIN

One or 2 per cent of individuals given penicillin develop manifestations of hypersensitivity.[218, 394] Urticaria and other benign types of skin rash predominate, but fatal cases of anaphylactic shock,[405, 427] exfoliative dermatitis[308] and acute vasculitis[31] also have been reported. The recent successful demonstration of circulating antibody to penicillin, by the passive transfer technic of Prausnitz and Küstner,[406] confirms the general impression that these reactions are allergic in nature.

Jaundice, which is a rare complication of penicillin therapy, has been reported in association with exfoliative dermatitis.[308] Presumably, it is due to some type of hypersensitivity reaction in the liver, although autopsy confirmation is not yet available. It is highly improbable that it is of toxic origin, since penicillin does not produce hepatic lesions in animals.[5, 159]

STREPTOMYCIN

A variety of drug reactions may occur during streptomycin therapy.[315] Some, such as disturbances of the eighth nerve and its nuclei, are clearly toxic in origin, while others, such as rash, fever and eosinophilia, are almost certainly manifestations of drug sensitization. The pathogenesis of the renal failure and the bone marrow depression that occur occasionally is not known.

Several instances of jaundice have been reported following streptomycin therapy.[315] Unfortunately, insufficient data are available to state whether these were due to an incidental infection with the hepatitis virus, a toxic reaction or the development of hypersensitivity. However, animal experiments[268] and studies of hepatic function[315] and morphology[437] in man suggest that streptomycin is not a hepatotoxin, and that if jaundice occurs during treatment it is likely to be due to a hypersensitivity reaction, or to syringe-transmitted viral hepatitis.

ANTICONVULSANTS AND SEDATIVES

CHLORPROMAZINE

(Thorazine, Largactil, 10-(3-dimethyl-
aminopropyl)-2-chlorphenothiazine
hydrochloride)

This drug has proved to be useful in the management of nausea and vomiting, certain emotional and mental disturbances, alcoholism and intractable pain and hiccup. Unfortunately, it also has a number of undesirable side effects, some clearly related to its pharmacologic actions, others to its toxicity or to the development of drug sensitization. The former include drowsiness, postural hypotension, dizziness and tachycardia; the latter, fever, pruritus, jaundice and, more rarely, rash, leukopenia and agranulocytosis. Since large doses of the drug do not produce liver injury or bone-marrow depression in animals,[368] and since the development of these complications in man is occasionally accompanied by fever, rash and eosinophilia,[368] it is highly probable that such reactions are manifestations of drug sensitization.

Chlorpromazine produces a type of hepatitis which is reminiscent of methyl testosterone jaundice[418] in that it simulates an extrahepatic biliary obstruction not only in its clinical and laboratory features but also in its histopathology.[36, 63, 101, 202, 276] The onset is usually abrupt with fever and mild constitutional symptoms and is followed in 1 to 4 days by jaundice, dark urine and clay-colored stools. Pruritus may precede the development of jaundice and is often a troublesome late manifestation. Anorexia, nausea and vomiting occur in some cases but are seldom severe. Hepatic enlargement and tenderness are inconstant findings. Characteristically, the urine contains bile, and the serum shows a sharp rise in its bilirubin and alkaline phosphatase content. In contrast, th thymol turbidity and the cephalin-cholestero flocculation reactions are usually norma The intensity and the duration of the jaundice are variable. However, it is seldom severe and rarely lasts longer than 4 week The patients usually are not very ill and g on to full recovery without residuals. However, one fatality has been reported.[36] In th instance the hepatitis was complicated b congestive failure and chronic passive congestion of the liver, so that the drug may n have been wholly responsible for death.

The outstanding findings on liver biop are the presence of numerous intracanalicul "bile thrombi" and bile-staining of the pare chymal and the Kupffer cells of the centr lobular zones. In addition, some specime also show minute foci of parenchymal necr and a mild periportal inflammatory reac- n characterized by a polymorphonuclear l eosinophilic exudate.[92] The fatal case viously mentioned[36] showed the same e of bile stasis plus extensive centrilobular rosis.*

From the reports available in the literature is difficult to estimate the incidence of orpromazine hepatitis. In some series[36, 202] jaundice has occurred in from 1 to 4 cent of patients receiving the drug, while others[276] the incidence has been 0.2 per nt or less. The development of hepatitis es not appear to be related to the dose el, the duration of therapy or the route of ministration. However, it has not been re- rted following single doses, and only rarely es it occur in individuals who have re- ved the drug for less than a week. Usually, jaundice develops between the second d fourth weeks of therapy. However, it y be delayed for a week or two following hdrawal of the drug,[101] an observation nsistent with the impression that the hepa- s is a manifestation of drug sensitization. interest in this connection is the fact that umption of therapy following an attack y produce a second reaction,[127] although does not always do so.[101]

Some toxicity studies in man[275] have led to demonstrate alterations in hepatic nction, even in individuals with pre- stent abnormalities. However, this has not en the experience of all investigators, omsulphalein retention having been noted a number of subjects who have not gone to develop jaundice.[127]

Chlorpromazine is alleged to yield false sitive tests for bilirubinuria in the Gmelin d “Ictotest” tablet reactions.[368] However, has been found in this laboratory that ile high concentrations of the drug react the latter, the red color produced es not resemble that of the bilirubin re- tion.

DILANTIN

(Sodium Diphenyl-Hydantoinate)

Approximately 15 per cent of epileptics maintained on Dilantin therapy for prolonged periods develop drug reactions. Those relating to the gums, the central nervous system and the gastro-intestinal tract are almost certainly of toxic origin and usually can be controlled by adjustment of the dosage. Skin reactions, on the other hand, which often are accompanied by fever and other constitutional symptoms, appear to be manifestations of drug hypersensitivity and are far more serious. Although they often subside despite continued drug administration, they occasionally give rise to exfoliative dermatitis[59, 243, 401] or hemorrhagic erythema multiforme[324] and terminate fatally.

At least two instances of hepatitis have been reported in nonfatal cases of exfoliative dermatitis due to Dilantin. In one[59] there was jaundice and hepatomegaly; in the other,[243] hepatosplenomegaly alone. Recovery ensued within a period of 6 weeks in both cases. Hepatic lesions have been observed also in fatal cases that have had no clinical signs of liver disease antemortem. In one,[401] exfoliative dermatitis was associated with typical periarteritis nodosa. The liver showed not only necrosis of the arterioles but also granuloma formation in the portal triads, and areas of necrosis in the adjacent parenchyma. In another,[324] there was simple fatty metamorphosis.

NIRVANOL

(Phenyl-ethyl-hydantoin)

Nirvanol, a compound closely related to Dilantin was once widely used as a sedative, and in the treatment of chorea.[105] It regularly produces a typical sensitization reaction, characterized by fever, rash and eosinophilia, in 1 to 2 weeks. Occasionally, the reaction is severe and terminates fatally, so that the drug has been abandoned in this country. Agranulocytosis and autopsy evidence of liver injury have been described, but no instances of clinically detectable hepatitis have been reported.

MESANTOIN

(3 methyl, 5,5-ethyl-phenyl-hydantoin)

Mesantoin, another compound closely related to Dilantin, also produces manifestations suggestive of drug hypersensitivity usually is associated with anorexia, nausea and vomiting. The liver tends to enlarge, the spleen is occasionally palpable, and itching is common. As the jaundice deepens, the stools become clay-colored, and the urine dark. Of special interest is the fact that the results of liver function tests, especially if carried out late in the disease, are more often suggestive of extrahepatic biliary obstruction than they are of hepatocellular damage. Thus, the serum alkaline phosphatase and cholesterol levels tend to be high, while the cephalin-cholesterol flocculation reaction is usually negative. Liver biopsy at this stage reveals pericholangitis and bile stasis, with little or no evidence of parenchymal injury, which has led to the suggestion that the jaundice may be due to an intrahepatic biliary obstruction (see pp. 335, 337). The course of the disease is variable. Although uneventful recovery may occur within a few weeks, often it is delayed for many months. Rarely, it is complicated by the development of hepatic fibrosis and xanthomatosis of the skin,[387] a syndrome difficult to distinguish from other types of biliary cirrhosis. (See Chap. 16, Biliary Cirrhosis.)

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* Through the courtesy of Dr. R. H. Boardman the Springfield Hospital, England, the writer had opportunity of reviewing the tissue sections in s case.

By far the most common type of hepatitis seen in individuals receiving any of the arsphenamines occurs from 3 to 18 months after the onset of treatment.[23, 372] There is now unequivocal experimental,[236] histologic[80] and epidemiologic[340] evidence to show that the liver injury in this instance is due not to drug toxicity but rather to accidental syringe-transmission of the hepatitis virus. No doubt most of the reported cases of massive hepatic necrosis[130] and postnecrotic cirrhosis[13, 80] following arsenotherapy also fall into this group.

In animals, high-protein and high-carbohydrate diets given *prophylactically* appear to protect against the hepatotoxic effects of arsenic.[69, 263] However, claims for the *therapeutic* efficacy of cysteine and methionine supplements in postarsphenamine jaundice are based on unconvincing clinical evidence.[293] Moreover, there would appear to be little logic in attempting to "detoxify" arsenic in this situation, since the jaundice is usually due to viral hepatitis or to a sensitization reaction.

The results of treatment with BAL have been equivocal.[95] Since BAL fixes and facilitates the removal of arsenic, it would appea to be a useful agent in the management o true arsenic intoxication, such as occurs afte massive arsphenamine therapy, and conceivably may be of value in sensitization reaction when traces of the drug still remain. However, it obviously has no place in the treatment of postarsphenamine jaundice due t the hepatitis virus. No doubt the inclusion o many such cases in treated groups has mad the evaluation of therapy difficult.

The inhalation of *arsine* (AsH_3, arsen uretted hydrogen) is usually followed by th development of jaundice, an effect due to a acute hemolytic reaction.

Atabrine

Prolonged administration of small suppressive doses of atabrine occasionally give rise to skin reactions. Rarely, these are accompanied by fulminant hepatitis, aplasti anemia or agranulocytosis.[224] Similar reactions also have been reported following intermittent therapeutic doses.[2] It is not know whether these are due to a toxic effect or t drug sensitization. The occasional occurrenc of positive patch tests,[2] and the fact that larg doses do not ordinarily cause any impairmen of hepatic function[49] are consistent with sensitization reaction. However, a dire toxic action cannot be excluded, since larg doses of atabrine are capable of producin hepatic necrosis in dogs.[49]

Bismuth

The only instances of hepatitis report following exposure to bismuth compoun have occurred in syphilitics given repeat injections over a long period of time.[283] D scriptions of the clinical features and certa epidemiologic data in these cases sugg syringe-transmission of the hepatitis virus.

Isonicotinic Acid Derivatives

Isoniazid (isonicotinic acid hydrazi Rimifon, Pyrizidin, Nydrazid) and ipro azid (1-isonicotinyl-2-isopropyl hydrazi Marsilid), recently developed agents used tuberculosis, are both potential hepatotoxi Prolonged administration of large doses isoniazid to animals (17.5 to 25.0 mg. Kg. for 4 to 5 weeks) produces jaundice a degeneration of both the hepatic paren- a and the proximal convoluted tubules kidney.[336] The jaundice is due, in part st, to a hemolysis.[29] The isopropyl de- ve is also toxic for the liver in rats and but does not produce hepatic injury in nonkey.[219]

erapeutic doses of isoniazid (2 to 10 per Kg. for 4 to 16 weeks) do not ordi- y affect hepatic function in man.[106, 327] ever, hepatitis has been reported as a complication. In one instance,[309] nausea, ache and rash occurred during the nth week of therapy. Jaundice, dark and acholic stools were noted 2 days . Biopsy of the liver on the fifth day aled periportal fibrosis, proliferation of ducts, a diffuse polymorphonuclear and hocytic inflammatory reaction and hep- llular vacuolization. These were inter- d as evidence of an acute drug hepatitis rimposed on a pre-existent cirrhosis, and suggestion was made that the latter was ably an important predisposing factor. ndice was still present at the end of 3 s but was fading. It is not clear from the presented whether the hepatitis in this was due to drug toxicity or to a sensitiza- reaction.

he isopropyl derivative, which is less toxic but more hemolytic in animals, has used in several patients with pre-existent osis and amyloidosis without producing ill effects.[219]

PARA-AMINOSALICYLIC ACID (PAS)

oth toxic and allergic reactions may com- ate the course of PAS therapy.[408] The ner, which are due almost certainly to local irritant action of the drug in the ro-intestinal tract, occur with great fre- ncy but seldom necessitate interruption reatment. The latter, which are far more ous, occur in approximately 2.5 per cent ndividuals. They usually appear between third and the sixth weeks of medication are characterized by fever, rash, eosino- lia and lymphadenopathy.[220, 408] Other common manifestations of hypersensitiv- include hepatitis,[72, 220, 258] Loeffler's syn- me,[408] neutropenia,[220] atypical lympho- osis[220] and renal damage.[72]

The onset of hepatitis is almost always preceded by the appearance of other manifestations of PAS sensitivity. The principal clinical features include jaundice, dark urine and enlargement and tenderness of the liver. Occasionally, hepatosplenomegaly occurs without jaundice.[220] Most cases show a marked increase in serum alkaline phosphatase, and abnormalities in the cephalin-cholesterol flocculation and thymol turbidity reactions.[220] Recovery usually ensues in from 4 to 5 weeks. The histologic picture in the liver has not been described. No fatalities have been reported to date.

Patch tests are occasionally positive,[72] confirming the impression that the hepatitis is a manifestation of drug hypersensitivity. Although active desensitization has apparently been accomplished successfully in a few instances[72, 408] it is difficult to exclude the possibility of spontaneous desensitization in such cases.[408] More often, reinstitution of therapy is followed promptly by a recurrence of symptoms.

PYRAZINAMIDE (ALDINAMIDE)

In combination with isoniazid, pyrazinamide is the most effective of the currently available antitubercular drugs. However, its usefulness is limited to some extent by its tendency to produce hepatitis when administered alone[296] or in combination with other drugs.[53, 252, 345] A recent review[277] indicates that jaundice occurs in approximately 3 per cent of patients receiving a daily dose of 40 mg. per kilogram of body weight. It is not known whether hepatic injury can be avoided by using smaller doses.

The hepatitis usually occurs late in the course of treatment, most commonly during the sixth month, but occasionally as early as the second. Its severity and duration are extremely variable, some cases developing very mild jaundice and subsiding within a week, others running a severe and prolonged course. One fatality has been reported,[252] and at least 2 others are known to have occurred.[253] In one severe case that recovered[252] intense jaundice and ascites were prominent features early in the disease.

Liver-function studies during the course of the jaundice are usually consistent with hepatocellular injury. A small number of patients on pyrazinamide have exhibited alterations in usually is associated with anorexia, nausea and vomiting. The liver tends to enlarge, the spleen is occasionally palpable, and itching is common. As the jaundice deepens, the stools become clay-colored, and the urine dark. Of special interest is the fact that the results of liver function tests, especially if carried out late in the disease, are more often suggestive of extrahepatic biliary obstruction than they are of hepatocellular damage. Thus, the serum alkaline phosphatase and cholesterol levels tend to be high, while the cephalin-cholesterol flocculation reaction is usually negative. Liver biopsy at this stage reveals pericholangitis and bile stasis, with little or no evidence of parenchymal injury, which has led to the suggestion that the jaundice may be due to an intrahepatic biliary obstruction (see pp. 335, 337). The course of the disease is variable. Although uneventful recovery may occur within a few weeks, often it is delayed for many months. Rarely, it is complicated by the development of hepatic fibrosis and xanthomatosis of the skin,[387] a syndrome difficult to distinguish from other types of biliary cirrhosis. (See Chap. 16, Biliary Cirrhosis.)

By far the most common type of hepatitis seen in individuals receiving any of the arsphenamines occurs from 3 to 18 months after the onset of treatment.[23, 372] There is now unequivocal experimental,[236] histologic[80] and epidemiologic[340] evidence to show that the liver injury in this instance is due not to drug toxicity but rather to accidental syringe-transmission of the hepatitis virus. No doubt most of the reported cases of massive hepatic necrosis[130] and postnecrotic cirrhosis[13, 80] following arsenotherapy also fall into this group.

In animals, high-protein and high-carbohydrate diets given *prophylactically* appear to protect against the hepatotoxic effects of arsenic.[69, 263] However, claims for the *therapeutic* efficacy of cysteine and methionine supplements in postarsphenamine jaundice are based on unconvincing clinical evidence.[293] Moreover, there would appear to be little logic in attempting to "detoxify" arsenic in this situation, since the jaundice is usually due to viral hepatitis or to a sensitization reaction.

The results of treatment with BAL have been equivocal.[95] Since BAL fixes and facilitates the removal of arsenic, it would appear to be a useful agent in the management of true arsenic intoxication, such as occurs after massive arsphenamine therapy, and conceivably may be of value in sensitization reactions when traces of the drug still remain. However, it obviously has no place in the treatment of postarsphenamine jaundice due to the hepatitis virus. No doubt the inclusion of many such cases in treated groups has made the evaluation of therapy difficult.

The inhalation of *arsine* (AsH_3, arsenuretted hydrogen) is usually followed by the development of jaundice, an effect due to an acute hemolytic reaction.

ATABRINE

Prolonged administration of small suppressive doses of atabrine occasionally gives rise to skin reactions. Rarely, these are accompanied by fulminant hepatitis, aplastic anemia or agranulocytosis.[224] Similar reactions also have been reported following intermittent therapeutic doses.[2] It is not known whether these are due to a toxic effect or to drug sensitization. The occasional occurrence of positive patch tests,[2] and the fact that large doses do not ordinarily cause any impairment of hepatic function[49] are consistent with a sensitization reaction. However, a direct toxic action cannot be excluded, since large doses of atabrine are capable of producing hepatic necrosis in dogs.[49]

BISMUTH

The only instances of hepatitis reported following exposure to bismuth compounds have occurred in syphilitics given repeated injections over a long period of time.[283] Descriptions of the clinical features and certain epidemiologic data in these cases suggest syringe-transmission of the hepatitis virus.

ISONICOTINIC ACID DERIVATIVES

Isoniazid (isonicotinic acid hydrazide, Rimifon, Pyrizidin, Nydrazid) and iproniazid (1-isonicotinyl-2-isopropyl hydrazine, Marsilid), recently developed agents used in tuberculosis, are both potential hepatotoxins. Prolonged administration of large doses of isoniazid to animals (17.5 to 25.0 mg. per Kg. for 4 to 5 weeks) produces jaundice and fatty degeneration of both the hepatic parenchyma and the proximal convoluted tubules in the kidney.[336] The jaundice is due, in part at least, to a hemolysis.[29] The isopropyl derivative is also toxic for the liver in rats and dogs but does not produce hepatic injury in the monkey.[219]

Therapeutic doses of isoniazid (2 to 10 mg. per Kg. for 4 to 16 weeks) do not ordinarily affect hepatic function in man.[106, 327] However, hepatitis has been reported as a rare complication. In one instance,[309] nausea, headache and rash occurred during the seventh week of therapy. Jaundice, dark urine and acholic stools were noted 2 days later. Biopsy of the liver on the fifth day revealed periportal fibrosis, proliferation of bile ducts, a diffuse polymorphonuclear and lymphocytic inflammatory reaction and hepatocellular vacuolization. These were interpreted as evidence of an acute drug hepatitis superimposed on a pre-existent cirrhosis, and the suggestion was made that the latter was probably an important predisposing factor. Jaundice was still present at the end of 3 weeks but was fading. It is not clear from the data presented whether the hepatitis in this case was due to drug toxicity or to a sensitization reaction.

The isopropyl derivative, which is less hepatoxic but more hemolytic in animals, has been used in several patients with pre-existent cirrhosis and amyloidosis without producing any ill effects.[219]

PARA-AMINOSALICYLIC ACID (PAS)

Both toxic and allergic reactions may complicate the course of PAS therapy.[408] The former, which are due almost certainly to the local irritant action of the drug in the gastro-intestinal tract, occur with great frequency but seldom necessitate interruption of treatment. The latter, which are far more serious, occur in approximately 2.5 per cent of individuals. They usually appear between the third and the sixth weeks of medication and are characterized by fever, rash, eosinophilia and lymphadenopathy.[220, 408] Other less common manifestations of hypersensitivity include hepatitis,[72, 220, 258] Loeffler's syndrome,[408] neutropenia,[220] atypical lymphocytosis[220] and renal damage.[72]

The onset of hepatitis is almost always preceded by the appearance of other manifestations of PAS sensitivity. The principal clinical features include jaundice, dark urine and enlargement and tenderness of the liver. Occasionally, hepatosplenomegaly occurs without jaundice.[220] Most cases show a marked increase in serum alkaline phosphatase, and abnormalities in the cephalin-cholesterol flocculation and thymol turbidity reactions.[220] Recovery usually ensues in from 4 to 5 weeks. The histologic picture in the liver has not been described. No fatalities have been reported to date.

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The hepatitis usually occurs late in the course of treatment, most commonly during the sixth month, but occasionally as early as the second. Its severity and duration are extremely variable, some cases developing very mild jaundice and subsiding within a week, others running a severe and prolonged course. One fatality has been reported,[252] and at least 2 others are known to have occurred.[253] In one severe case that recovered[252] intense jaundice and ascites were prominent features early in the disease.

Liver-function studies during the course of the jaundice are usually consistent with hepatocellular injury. A small number of patients on pyrazinamide have exhibited alterations in hepatic function without going on to develop jaundice.[252, 296] Biopsy of the liver in the severely jaundiced case with ascites mentioned above[252] revealed a marked inflammatory reaction in both the parenchyma and the portal tracts, areas of focal necrosis and signs of marked bile stasis.* The fatal case reported by McDermott et al.[252] died on the eighth day of illness and at autopsy showed massive hemorrhagic necrosis of the liver,* but no other significant lesions.

It is not known whether the hepatitis induced by pyrazinamide is due to a direct toxic action or is the result of a sensitization reaction. The fact that massive doses of the drug are capable of inducing hepatic necrosis in dogs,[325] and the fact that the drug is not known to produce other signs of drug sensitization make a direct toxic action the more likely mechanism. However, in occasional cases[53] recovery from hepatitis occurs despite continued drug administration, an observation difficult to explain in the case of a toxic reaction.

STILBAMIDINE

The 4:4′-diamidino derivatives of stilbene (stilbamidine), diphenyl ether (phenamidine), diphenoxy propane (propamidine) and diphenoxy pentane (pentamidine), agents once used exclusively in the treatment of trypanosomiasis[42] and leishmaniasis,[188] have been found recently to be of value in the management of multiple myeloma,[9] actinomycosis,[264] blastomycosis[344] and tic douloureux.[364] Because they are known to produce lesions in the liver and the kidneys of animals,[423] there has been concern over their possible toxic effects in man.

Transient vasomotor and gastro-intestinal symptoms often occur immediately following the first few injections of stilbamidine. These usually subside within a few minutes and may be avoided by injecting the drug slowly.[42, 188] Of greater importance is the dissociated sensory disturbance over the distribution of the trigeminal nerve that frequently follows prolonged therapy.[9, 188] The neuropathy usually appears from 2 to 3 months following cessation of medication and is due to a toxic degeneration of the principa sensory nucleus of the fifth cranial nerve.

Therapeutic doses of stilbamidine (2 to mg. per Kg. daily or every other day in amounts up to 6.0 Gm.) do not ordinaril cause any significant depression of hepati or renal function in man.[9] However, in experimental animals, larger doses have bee found to produce severe fatty infiltration o the liver, degeneration of the convolute tubules of the kidneys, and renal failure.[42 A number of years ago a fulminant type o hepatitis was observed in patients undergoin stilbamidine therapy for kala-azar in th Sudan.[188] Characteristically, the symptom occurred from 1 to 3 months following cessation of therapy. At autopsy, the outstandin findings were extensive centrilobular necros and fatty infiltration of the liver. In som cases, the lesions closely resembled those o acute yellow atrophy. The hepatitis was a tributed to an increase in the toxicity of th drug related to its storage and exposure t light. Subsequently, the increase in the toxi ity of stilbamidine on exposure to light wa confirmed in animals.[14, 124] However, in non of the experiments reported were the lon latent period and centrilobular hepatic n crosis reproduced. In retrospect, it is high probable that these deaths were due syringe-transmitted viral hepatitis, especial since the disease was known to be prevale in the Sudan at the time.

SULFONAMIDES

The sulfonamides fall into the category drugs capable of producing hepatic inju both by direct toxic action and by the indu tion of a hypersensitivity reaction. From clinical point of view, however, it is only t latter that gives rise to serious consequenc

Prolonged administration of sulfonamid to animals leads to the development of fo inflammatory, degenerative and necrotic sions in the liver, the kidneys, the myoc dium and the lungs.[75, 123] Similar lesions ha been observed in a high proportion of in viduals who have received sulfonami shortly before death.[123, 262] These are thou to be manifestations of true drug intoxi tion. The depression in hepatic function, and the occasional occurrence of hepatitis iduals without other signs of hypersensi- [409] have also been attributed to the toxic s of the drug. However, the fact that can seldom be correlated with the int of drug ingested raises the question hether they may not be related to some factor, such as infection or sensitiza-

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* These sections were made available to the writer through the courtesy of Dr. Walsh McDermott and Dr. Robert M. McCune, Jr., of the New York Hospital.

variable proportion of individuals, nding on the particular sulfonamide de- ive employed, develop a reaction char- ized by fever, rash and signs of visceral bone marrow injury. Although the clini- nanifestations often suggest involvement single organ, postmortem examination lly reveals widespread inflammatory and otic lesions in many of the viscera and d vessels.[122, 271] Occasionally, identical ns are found in individuals who have ived sulfonamides but who have not had cal manifestations of a drug reaction.[122]

clinical and morphologic features of reactions resemble those of serum sick- so closely that it is difficult to escape the lusion that they are allergic in nature,[156, 18] even though attempts to demonstrate ific antibodies have been unsuccessful.[156]

cute hepatitis occurs in about 0.6 cent of patients undergoing sulfanila- e therapy,[30, 58, 64, 113, 128, 156, 229, 271, 337] somewhat less frequently in individuals receive sulfathiazole,[58] sulfadiazine[58, 167] other sulfonamide derivatives. The inci- ce and the severity of the hepatitis cannot correlated with the amount of drug ad- istered. In most instances, the onset is in the first 2 weeks but may be delayed il the sixth week of therapy, or even r.[337] Rarely, hepatitis and other manifes- ons of sensitization do not become evident il a number of weeks have elapsed follow- cessation of medication.[128] Approxi- tely one quarter of these reactions occur individuals who have been exposed pre- usly to the drug.

The onset of symptoms is usually sudden, h fever, anorexia, nausea and vomiting, may be accompanied by a rash. Jaundice ears on the third to the sixth days, but y be delayed for as long as 2 weeks. The er enlarges and is usually tender. Occa- nally, there is also splenomegaly. Dark ne and acholic stools are the rule, at least early in the course. The laboratory features, which are those of hepatocellular damage, are not distinctive, except that the serum alkaline phosphatase level may be very high.[128] Most cases go on to slow recovery, but a few lapse into coma and die of hepatic failure.[30, 64, 128, 167, 271, 337] Death may occur as early as the fifth day[167] or may be delayed for several months.[30] Ascites is often present when the course is chronic. The writer has seen 2 instances of chronic hepatitis with progression to cirrhosis following sulfonamide therapy. Progressive enlargement of the liver, jaundice and ascites characterized the course in both, and death ensued in the second and the third years of illness, respectively. Serial biopsy specimens obtained in one revealed hepatic lesions consistent with a sensitization reaction.

Postmortem examination in individuals who die of hepatic failure usually reveals a small liver with evidence of massive necrosis of the parenchyma, collapse of the stroma and an inflammatory reaction in the portal triads.[30, 64, 167, 271] In contrast, individuals who die of more generalized reactions show only focal lesions in the liver. These include areas of hepatic necrosis, foci of inflammatory cells, and spotty necrosis of vessels. The exudate, which is composed of large mononuclear cells and a smaller number of plasma cells, eosinophils and polymorphonuclear cells, is predominantly perivascular and periportal in location.[122, 271] Similar lesions are also found in the myocardium, the kidneys, the bone marrow, the skin and other tissues.

It has been suggested that pre-existent hepatic disease renders the liver more susceptible to further injury by the sulfonamides.[58, 409] Autopsy experience does not bear this out. Moreover, there is no clinical evidence to indicate that sulfonamides increase hepatic dysfunction in such individuals.[294] However, cirrhotics appear to be peculiarly susceptible to the *other* toxic effects of sulfonamides, particularly in the kidney.[198, 294] Therefore, it is probably wise to avoid their use in patients with liver disease.

In passing, it should be noted that acute hemolytic reactions occasionally follow the ingestion of the sulfonamides and give rise to jaundice, which may be mistaken for a manifestation of hepatitis. These occur early in the course of treatment and especially after sulfanilamide and sulfapyridine.[229]

The etiology of the renal complications of sulfonamide therapy is complex. Some lesions are due to the mechanical effects of precipitated drug crystals, others to the toxic action of the drug, and finally there are those due to sensitization reactions. It is the last type that is most often associated with drug hepatitis.

TIBIONE
(Amithiozone, *p*-Acetylaminobenzaldehyde Thiosemicarbazone)

Tibione, one of the newer drugs used in the treatment of tuberculosis, is generally regarded as a potential hepatotoxin. Although minor alterations in hepatic function[77] and fatty infiltration of the liver[109] have been described as toxic effects, there have been no reports of acute hepatitis. The other manifestations of toxicity, which include nausea, vomiting, rash[77] and agranulocytosis,[306] suggest that the drug may be a sensitizing agent. This is consistent with the observation that even massive doses fail to produce parenchymatous or bone marrow lesions in animals.[306, 373]

Similar alterations in hepatic function and symptoms of sensitization have been observed following the administration of Myvizone (p-formylacetanilide thiosemicarbazone), a compound closely related to tibione.[361]

CHEMOTHERAPEUTIC AGENTS USED IN MALIGNANT DISEASE

NITROGEN MUSTARD
(Methyl-Bis[(β-Chlorethyl)]Amine

The principal toxic effect of nitrogen mustard is depression of the bone marrow. This is seen not only in man but also in all other species studied.[146] In the cat, nitrogen mustard also produces focal areas of hepatic necrosis,[440] but in most other animals the liver is not affected.[146] There is still some uncertainty regarding the possible hepatotoxic effects of the drug in man. In one study,[73] 3 out of 50 treated patients with Hodgkin's disease showed miliary foci of hepatic necrosis at autopsy, and 2 of the 4 cases with jaundice appeared to get worse under treatmen effects which were attributed to drug toxicit However, in another investigation,[441] tests o hepatic function and needle biopsy of th liver failed to show any evidence of live damage that could be ascribed to chemo therapy. Moreover, the clinical and func tional status of the liver appeared to improv in those cases with antecedent hepatic involvement.

Obviously, it is difficult to interpret th histologic and functional changes in a live that is already the site of lymphomatous infiltration. Although the possibility of hepatotoxic action cannot be excluded, th benefits to be derived from nitrogen mustar far outweigh its possible dangers, so that th presence of hepatic lesions is not a contraindication to therapy.

TRIETHYLENE MELAMINE (TEM)

This agent shares the bone-marrow depressant properties of nitrogen mustar but does not produce hepatic injury.[187]

URETHANE (ETHYL CARBAMATE)

Patients undergoing prolonged therap with urethane occasionally develop hepat necrosis, manifested clinically by hepat megaly, ascites and jaundice.[261, 284] At a topsy, the liver is enlarged and exhibits e tensive centrilobular hepatocellular necros atrophy and vacuolization, and marked su intimal edema and necrosis of the centr veins. Except for the changes in the vei the lesion resembles that of severe passi congestion. Careful study of the lesion experimental animals indicates that t hepatocellular changes are secondary to va cular injury, with resultant extravasation edema fluid and blood around the branch of the portal vein and between the sinuso and the parenchymal cells.[83]

Other manifestations of urethane toxic include gastro-intestinal disturbances, pression of the bone marrow and re damage.[284]

HORMONAL AND METABOLIC AGENTS

ANTITHYROID DRUGS

Thiouracil,[125, 126, 175, 289] **propylthioura**

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DINITROPHENOL

ccasionally, small doses of dinitrophenol luce an acute hepatitis.[160, 359] Although as not been possible to demonstrate skin itivity or the presence of circulatory anti- ies in such cases,[247] it is highly probable the hepatitis is due to drug hypersensi- y. The reasons for believing so include following: (1) the hepatitis occasionally ssociated with an urticarial rash;[359] (2) clinical and laboratory features closely mble those seen in the hypersensitivity e of arsenical hepatitis;[359] (3) even fatal es of dinitrophenol do not ordinarily duce significant alterations in the liver, er in experimental animals[391] or in n;[301, 392] and (4) other common manifes- ons of drug hypersensitivity, including ioneurotic edema, neutropenia, renal in- y and arthritis, have been reported.[7, 235]

Large doses of dinitrophenol often stain tissues yellow due to the color of the g itself. This must be distinguished from e icterus.

METHYL TESTOSTERONE

An unusual obstructivelike jaundice is seen occasionally during methyl testosterone therapy.[44, 418] Histologically, the liver shows marked centrilobular bile stasis with little or no evidence of parenchymal damage. In contrast with other types of drug hepatitis, there is no inflammatory reaction, either in the parenchyma or the portal zones. The results of liver function tests are consistent with the histologic evidence of bile stasis and little or no injury to the parenchyma. On the basis of these findings, it has been suggested that the jaundice is due to interference with the free flow of bile in the canaliculi related to an increase in its viscidity, and that the latter is the consequence of a disturbance in bile hydration due to mild hepatocellular injury.[418] This interpretation is open to question, since localized obstructions within the intrahepatic biliary system do not produce jaundice unless the drainage from a considerable fraction of the parenchyma is blocked. It is more likely that the jaundice is due to retention of bilirubin secondary to generalized hepatocellular injury, and that the intracanalicular thrombi are merely an expression of local stasis of bile. The absence of histologically demonstrable changes in the parenchymal cells does not exclude a functional excretory disturbance, and, indeed, a similar type of jaundice is seen frequently in Weil's disease.

Little is known about the pathogenesis of the hepatic injury produced by methyl testosterone. The fact that the jaundice occurs only sporadically without relation to the amount of drug administered and is not reproducible in animals suggests the possibility of drug sensitization. However, the histologic features are not consistent, no other manifestations of hypersensitivity have been observed, and resumption of methyl testosterone therapy following recovery does not precipitate a relapse.[418]

Symptoms usually appear between the second and the fifth months of medication, although they may occur as early as the eighth day. The onset is characterized by malaise, nausea and other disturbances of the gastro-intestinal tract. Jaundice follows in from 1 to 4 weeks and is accompanied by manifestation of hepatitis. These occur early in the course of treatment and especially after sulfanilamide and sulfapyridine.[229]

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Obviously, it is difficult to interpret the histologic and functional changes in a liver that is already the site of lymphomatous infiltration. Although the possibility of a hepatotoxic action cannot be excluded, the benefits to be derived from nitrogen mustard far outweigh its possible dangers, so that the presence of hepatic lesions is not a contraindication to therapy.

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Other manifestations of urethane toxicity include gastro-intestinal disturbances, depression of the bone marrow and renal damage.[284]

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Hepatitis usually occurs in association with other signs of sensitization. The clinical and morphologic features resemble those in the sensitization type of arsenical hepatitis (see p. 363). Fatal cases usually succumb within 2 weeks and show necrosis of vessels and a perivascular inflammatory reaction in the portal triads.[134, 251] Occasionally, death is delayed for several weeks. In one such case, the liver was small and exhibited areas of focal and central necrosis, central bile pigmentation and bile thrombi.[175]

Tapazole (Methimazole, 1-methyl-2-mercaptoimidazole), the most recent of the antithyroid drugs, also appears to be a sensitizing agent. It produces rash and urticaria in approximately 5 per cent of patients,[18] and recently has been responsible for a nonfatal case of hepatitis and agranulocytosis.[329]

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Little is known about the pathogenesis of the hepatic injury produced by methyl testosterone. The fact that the jaundice occurs only sporadically without relation to the amount of drug administered and is not reproducible in animals suggests the possibility of drug sensitization. However, the histologic features are not consistent, no other manifestations of hypersensitivity have been observed, and resumption of methyl testosterone therapy following recovery does not precipitate a relapse.[418]

Symptoms usually appear between the second and the fifth months of medication, although they may occur as early as the eighth day. The onset is characterized by malaise, nausea and other disturbances of the gastro-intestinal tract. Jaundice follows in from 1 to 4 weeks and is accompanied by count satisfactorily for all the types of liver injury encountered in hyperthyroidism.

The clinical significance of these hepatic lesions is difficult to evaluate. Ordinarily, they give rise to no overt signs of liver disease, except for occasional hepatomegaly, but in approximately 20 per cent of fatal cases they produce jaundice.[24] Therefore, it would seem reasonable to assume that when the lesions are extensive they may contribute to a fatal outcome. At one time, it was believed that they were responsible for thyrotoxic crises. However, this view had to be abandoned for lack of supporting evidence.[255]

PREGNANCY

Much has been written about the strain imposed upon the liver by normal pregnancy. However, there is neither chemical[71] nor histologic[184, 282] evidence that the liver suffers any injury as a consequence of the increased demands made upon it. Also, interest has centered on the liver in connection with its possible role in the pathogenesis of certain complications of pregnancy. Although a variety of hepatic lesions have been described in eclampsia, hyperemesis gravidarum and other toxemias, it is now believed that they are the consequence and not the cause of these complications. However, there are 3 types of liver injury that present as primary disorders. These include: (1) obstetric acute yellow atrophy, a distinct morphologic entity apparently related to the gravid state, or some complication thereof, (2) massive hepatic necrosis, now known to be a manifestation of an intercurrent infection with the hepatitis virus and (3) zonal hepatic necrosis due to chloroform anesthesia. All three of these produce similar clinical manifestations but can be readily differentiated on the basis of their characteristic histologic features. Much of the confusion in the older literature stemmed from a failure to distinguish between these unrelated types of liver disease.

ECLAMPSIA

The hepatic lesion seen most frequently in eclampsia is a peripheral hemorrhagic necrosis of the lobules. Although generally considered pathognomonic of the disease when present, the lesion is found in only half the cases that come to autopsy.[393] Moreo its specificity may be questioned, sinc wide variety of other histologic changes h been described.[26] Some investigators[185] (phasize the importance of fibrin thromb the peripheral lobular capillaries and sug that they are responsible for both the hem rhagic necrosis and occasional instances infarction that occur in eclampsia. It is g erally agreed, however, that, whatever t pathogenesis, the development of hep lesions is a terminal event, probably oc ring at the time of the convulsions.[183] The clinical significance of these change difficult to evaluate, although the absenc jaundice suggests that functional impairm is usually not severe, and that the hep lesion is not responsible for either the c vulsions or the fatal outcome.

PRE-ECLAMPSIA AND OTHER NONCONVULSIVE TOXEMIAS

Minor abnormalities of liver function often demonstrable in most toxemias of p nancy and, in general, can be correlated the severity of the underlying disease.[71] H ever, liver biopsy studies have failed to veal any significant structural changes,[18 that it is doubtful that the impairmen function has any clinical significance.

HYPEREMESIS GRAVIDARUM

There is a pernicious form of vom that occurs early in pregnancy, usually tween the fourth and the eighth weeks, w is difficult to control and which occasio terminates fatally between the ninth an twenty-second weeks. Mild jaundice appears when vomiting has persisted longer than 6 weeks.[354] Interruption pregnancy usually terminates the attack may not. The etiology of this syndron not known but has been ascribed vari to reflex, neurotic, toxic and meta disturbances.[354, 375, 428]

In fatal cases, the liver invariably s marked fatty infiltration, especially in central zone of the lobules. It is highly able that this is a starvation effect and the consequence of an intoxication.[35 pairment of hepatic function parallel severity of the symptoms and appears related to the lesions described.[343] Are ral necrosis have also been reported in w instances[428] and have been cited as ence that hyperemesis gravidarum is due an intoxication.[173, 428] However, it has n pointed out that chloroform anesthesia been employed in many of these cases probably accounts for the necrosis.[354]

Vomiting of Late Pregnancy[354]

)ccasionally, there is a sudden onset of ere vomiting late in pregnancy. Although is usually due to the development of a nplication, such as pyelitis or acute yel- atrophy, there may be no demonstrable se. The symptoms in the idiopathic type y be severe and culminate in death. At opsy, the findings are identical with those hyperemesis gravidarum. Only those indi- uals who have been subjected to chloro- m anesthesia show centrilobular hepatic rosis.

ute Yellow Atrophy of Pregnancy

This entity is to be distinguished from ssical acute yellow atrophy, the type massive hepatic necrosis due to intercur- t infection with the hepatitis virus. Al- ugh the clinical features in the two dis- es are almost identical, their morphologic racteristics are so different that it is dly likely that they represent variants of same disease.[355] There is evidence to licate that the obstetric type occurs far re frequently than the viral. The impres- n that the syndrome of acute yellow atro- y in pregnancy is usually due to a viral ection is based on reports of its frequent currence in women during epidemics of ectious hepatitis.[171] Although this evidence nnot be dismissed, it is noteworthy that the ne relationship has not been observed ce the turn of the century. Indeed, recent ports indicate that viral hepatitis usually as a benign course in pregnancy, although may increase the risk of spontaneous abor- n and stillbirth.[334] Perhaps the decline in al massive hepatic necrosis can be ascribed the improvement in prenatal nutritional ndards. Acute yellow atrophy of preg- ncy comes on abruptly during the ninth onth and is characterized clinically by se- re vomiting and epigastric pain, followed thin a few days by jaundice. The symptoms increase rapidly in severity, the jaundice becoming intense and the vomitus coffee-ground in nature. Spontaneous delivery of a dead fetus usually occurs between the seventh and the twelfth days and is followed within 3 days by coma and death. Occasionally, there are convulsions, hypertension, edema and albuminuria.

Characteristically, the liver is found to be small in size and yellow in color. Microscopically, there is an intense fatty infiltration of the parenchymal cells save for a small rim around the portal tracts. In contradistinction to the viral type of acute yellow atrophy, there is no necrosis and little or no inflammatory reaction.[355] The suggestion has been made that the fatty infiltration may represent an early phase of toxic necrosis.[377] However, it is well known that in other forms of toxic hepatitis in which fatty infiltration precedes necrosis, the necrosis is almost always evident by the second or the third day, while, in the present instance, fatty infiltration persists without necrosis for as long as 14 days.[355]

Although the disease is usually fatal, the pathologic picture suggests that the lesion is reversible, and, indeed, there is one recorded instance of recovery in which the diagnosis was confirmed by serial biopsies of the liver.[420]

The etiology of this syndrome is unknown. Toxic and metabolic factors have been postulated, but none have been demonstrated. Whatever the pathogenesis of the lesion, it appears to be directly responsible for the hepatic insufficiency and the fatal outcome that ensue.

The differentiation between obstetric acute yellow atrophy, fulminant viral hepatitis and chloroform poisoning is usually impossible on clinical grounds alone and depends on the morphologic features which have been described. It is of interest that the hepatic necrosis in chloroform poisoning, which is ordinarily of the centrilobular type, may be midzonal when it occurs during pregnancy.[355]

MISCELLANEOUS

Burns and Tannic Acid

A variety of hepatic lesions have been observed in individuals with extensive burns.[27, [136, 431] It is now clear from the results of animal experiments[12, 116, 164] that most of these can be attributed to tannic acid therapy and possibly to infection. In dogs, extensive burns of the skin, if left untreated, are usually accompanied by central congestion and atrophy of the hepatic parenchyma. However, if infection supervenes, or if tannic acid dressings are applied, central necrosis of the liver ensues.[164] That the presence of a burn is not essential for this effect is evident from the demonstration that the same lesions occur when tannic acid is injected subcutaneously into normal animals.[12, 116, 164]

Severe liver damage, occasionally accompanied by jaundice and ascites, is also seen in patients with fatal burns that have been treated with tannic acid. The midzonal necrosis and the Councilman bodies found in such cases closely resemble those of yellow fever.[27] In contrast, untreated cases show only minor alterations in the staining quality of the parenchymal cells, varying degrees of fatty infiltration and centrilobular atrophy without necrosis.[136] Impairment of hepatic function also has been reported following burns.[431] However, it is not clear from the data presented whether this occurs in the absence of infection and tannic acid therapy.

Ethyl Alcohol

It is generally agreed that alcohol is not a hepatotoxin, despite the well-documented evidence that its long-continued ingestion is related in some way to the development of Laennec's cirrhosis, and that it is capable of acting synergistically with certain known hepatotoxins. At the present time it is believed that Laennec's cirrhosis is a manifestation of a specific type of nutritional deficiency, and that chronic alcoholism plays no direct role in its pathogenesis but merely encourages a poor dietary intake. Recently, however, suggestive experimental evidence has been presented to show that alcohol may exert a more direct effect by creating a relative choline deficiency. This has been attributed to the decrease in the choline:calorie ratio of the diet when alcohol calories are added.[32] However, this interpretation may be questioned, since, under experimental conditions which permit no change in this ratio, alcohol still appears to increase the require-
ment for choline.[192, 193] The reader is refer
to a recent review[189] for a more deta
analysis of the interrelationships between
cohol ingestion, the dietary intake and
rhosis, and to a previous section of this ch
ter for a discussion of the potentiating ef
of alcohol on the hepatotoxic actions of o
agents.

Liver Extract

Liver extract is said to produce a typ
toxic hepatitis that has many of the cli
features of infectious hepatitis.[100] Sinc
of the cases reported have occurred in c
patients undergoing long-term treatment
pernicious anemia with intramuscular in
tions of liver extract, it is possible that
hepatitis encountered is not a manifest
of drug intoxication but rather the result
syringe-transmitted viral infection. Alth
liver extract occasionally produces sensi
tion reactions,[260] hepatitis has not been
ported as one of its features.

Phenylhydrazine

The jaundice seen during phenylhydr
therapy for polycythemia vera is due
marily to the rapid hemolysis of erythroc
It has been suggested that prolonged o
cessive treatment may also result in
injury. This is based on the observation
massive doses produce fatty degeneration
centrilobular necrosis of the liver in rabb
and that following repeated courses of t
ment occasional patients develop cirrhos
However, it has been shown that even
longed administration of therapeutic
does not impair hepatic function, eith
man[45] or in animals,[135] and that the
following such treatment shows no ch
other than mild hemosiderosis.[4] As fo
development of cirrhosis, there is no r
to implicate phenylhydrazine as the etio
factor, since the lesion is known to
spontaneously in untreated cases of
cythemia vera.

Pyridine

At one time, pyridine was used thera
cally in the management of convulsive
zures and asthma and still is employed w
in industry as a solvent and as a reag

e synthesis of certain organic compounds. is capable of producing severe hepatic and nal injury in man,[300] but the lesions have ot been described. In the rat, pyridine pro-uces both fatty infiltration and acute hepatic ecrosis and, following prolonged adminis-ation, may give rise to cirrhosis.[20] Methio-ine and choline partially protect against the tty infiltration and fibrosis but do not pre-ent the necrosis. It has been suggested, herefore, that pyridine injures the liver, both y a direct toxic action and by producing an ntrinsic nutritional deficiency, possibly by iverting methyl groups during its methyla-ion.

RADIATION

Irradiation of the liver with roentgen rays rovokes more intense and more immediate adiation sickness than treatment over any ther area of the body. However, the symp-oms do not appear to be correlated with any ignificant impairment of hepatic function.[298] The effect of therapeutic doses on the morphology of the liver in man are not known, although it is generally stated that the hepatic cells are capable of tolerating enormous doses. In the few instances of hepatic damage reported following intensive irradiation, the epithelium of the small and the medium-sized bile ducts has been the site of severe degeneration and necrosis, while the parenchymal cells have been largely spared.[57] However, in animals, the parenchymal cells appear to be far more sensitive than the biliary epithelium.[10] Two types of change have been described in the liver following massive experimental irradiation: (1) varying degrees of edema, hyperemia and leukocytic infiltration, interpreted as evidence of vascular damage, and (2) degeneration and necrosis of hepatic cells.[10] Very large doses are required to provoke necrosis, but relatively small ones are capable of producing more subtle changes in the cytoplasm.[226, 430] It has been pointed out that the hepatic changes are more marked after total body irradiation than after local irradiation over the liver, and that the lesions closely resemble those produced by histamine. This has led to the suggestion that the effects of x-rays on the liver may be an indirect one, mediated through histamine-like substances liberated elsewhere in the body.[103]

Surprisingly few changes in the liver have been observed in *atom bomb casualties.*[223] In individuals who have survived for less than 6 weeks, the principal findings have been central congestion with atrophy of the hepatic cords, and edema of the central veins. In those who have survived longer, the liver has been the site of fatty infiltration, a change thought to be due to malnutrition rather than to irradiation.

It is worthy of note that at least 2 radioactive materials used as therapeutic or diagnostic agents are capable of producing liver injury: radioactive colloidal gold and thorium dioxide (Thorotrast).

Although there are no clinical reports of liver injury following the use of radioactive colloidal gold, it is known to produce severe midzonal hepatic necrosis in rats.[195] The architecture of the liver is grossly distorted, both by necrosis and by the transformation of the parenchyma to masses of bizarre giant cells. Although the lesion may resemble cirrhosis, there is no fibrosis. Clinically, the animals exhibit jaundice and ascites before they die. Survival varies from a few days to 7 months.

Despite some claims to the contrary,[435, 436] it is generally agreed that Thorotrast produces liver injury, and that it may be a carcinogen.[395] It has been estimated that approximately 25 per cent of individuals who receive the large doses of colloidal thorium dioxide required for hepatosplenography develop fibrosis of the liver.[395] In animals, similar doses produce focal hepatic necrosis and proliferation of connective tissue.[287] Five instances of malignancy, 3 of them in the liver, have been reported following injections of Thorotrast, and tumors have been induced in animals in a similar manner.[395] Although the low incidence of malignancy suggests that Thorotrast may have only slight carcinogenic activity in man, it should be borne in mind that relatively few individuals who have received Thorotrast have survived for sufficiently long periods to develop tumors.

All of the injected thorium dioxide is retained in the reticuloendothelium, and especially in the liver and the spleen. Over a period of years, some may shift from the liver and the spleen to adjacent lymph nodes, but none is excreted. Although large particles can be demonstrated in the Kupffer cells of the liver and in the reticuloendothelium of the spleen, it is generally believed that the fibrosis that occurs in these organs is due to radioactivity and not to a foreign-body reaction. The 75 ml. dose of 25 per cent thorium dioxide solution required for hepatosplenography has been estimated to possess an alpha ray activity equivalent to that of 1.5 to 3.0 micrograms of radium.[436] In the course of its degradation, a series of other radioactive elements are produced, some of which emit beta and gamma rays in small quantity. Several of these have been identified in the excreta and the expired air many years after the injection of Thorotrast.[380] The alleged carcinogenic potentiality of Thorotrast is also presumed to be related to its radioactivity.

TRANSFUSION REACTIONS

Not infrequently, severe transfusion r
tions are accompanied by jaundice, a m
festation almost certainly due to acute
molysis. However, there is evidence to
gest that hepatic injury may play a cont
tory role. In most fatal cases, the liver sh
areas of central necrosis,[40, 140] and sin
lesions have been produced in dogs by
jecting heterologous hemagglutinins.[290]
of interest that healing is followed by di
fibrosis in animals that survive, but a sin
sequence has not been described in man

The pathogenesis of the hepatic lesion
transfusion reactions is not well underst
Possibly they are related to shock whi
often present. It has also been suggested
they may be the result of impaction o
sinusoids with agglutinated erythrocyte

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Chapter 13

HEPATITIS ASSOCIATED WITH SYSTEMIC INFECTIONS

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Many systemic infections produce structural and functional changes in the liver which are occasionally accompanied by jaundice. Fortunately, these are seldom of sufficient severity to alter the course of the underlying disease or to require special treatment. It is important to note, however, that, unless their relationship to infection is recognized, they may lead to serious diagnostic errors. Jaundice is particularly likely to be misleading, since it may be misinterpreted as a sign of primary hepatic or biliary tract disease and thus divert attention from the underlying infection and lead to inappropriate treatment.

Although the pathogenesis of the hepatic injury in infection is obscure in many instances, the following mechanisms are known to be of importance in some: (1) direct invasion of the parenchyma by blood-borne or lymph-borne infectious agents, (2) hepatocellular injury by known or presumed circulating toxins and (3) nonspecific injury to the liver related to hyperpyrexia, malnutrition and anoxemia. Considering the importance of the liver in clearing the blood of circulating organisms,[15] it might be anticipated that many instances of hepatitis would be the result of direct invasion by infectious agents. Actually, however, organisms seldom can be demonstrated in the liver. Of course, that does not preclude the possibility that organisms engulfed by the liver produce hepatocellular injury and then undergo dissolution. The experimental observation that intraportally injected streptococci induce an acute hepatitis and then vanish[107] would appear to be consistent with such a mechanism. However, it is generally believed that most instances of hepatic injury associated with infection are of toxic origin. Although circulating toxins have not been demonstrated in most cases, the cell bodies of certain bacteria are known to contain endotoxins capable of producing liver damage.[122]

In evaluating the role of infection in the pathogenesis of hepatic injury, due consideration must be given to the nonspecific effects of fever, anoxemia and malnutrition. These often contribute to the depression in hepatic function and may be responsible for some of the lesions found in the liver. However, they seldom give rise to jaundice.

Since many bacteria are capable of hemolyzing red cells in culture media, the question often arises whether hemolysis plays any role in the jaundice associated with infection. In the case of *Clostridium welchii* sepsis, the evidence is clear that hemolysis is the principal factor responsible for jaundice. However, its importance in other infections is still in doubt, especially since the frequency and the severity of the jaundice seldom can be correlated with the hemolytic properties of the organism involved.

Infection often provokes an exacerbation of symptoms in patients with chronic liver disease. The reason for this is not clear, although experimental evidence indicates that the injured liver is unusually susceptible to the toxic effects of infection.[125] Therefore, it is important to search for signs of antecedent liver disease whenever jaundice appears during the course of an infection.

A great many infections are accompanied by alterations in the serum protein pattern which may affect the results of the thymol turbidity, the cephalin-cholesterol flocculation and other similar reactions often erroneously regarded as specific tests of liver function. It should be emphasized that these are not necessarily related to liver injury, so that the results of turbidity and flocculation tests must be interpreted with caution in the face of infection. A nonspecific effect should be suspected whenever the abnormalities in "liver function" are limited to the results of tests dependent on the serum protein pattern.

BACTERIAL INFECTIONS

PNEUMOCOCCUS

Most, if not all, patients with lobar pneumonia exhibit impairment of hepatic function,[46, 186] and from 3 to 24 per cent develop jaundice.[46, 93, 142, 186] It is highly probable that the hepatocellular injury responsible for these manifestations is due primarily to the toxic effects of the underlying pneumococcal infection, an interpretation consistent with the observation that a similar type of liver damage occurs in pneumococcal peritonitis and sepsis.[9] Fever and anoxemia are probably contributory factors, although they seldom can be correlated with the degree of hepatic dysfunction present.[186]

It is reasonable to suppose that the occurrence of jaundice merely signifies a more severe grade of hepatocellular injury than is usually present in pneumonia. However, it has been suggested that increased hemolysis may be a factor, an opinion based on the observation that the fecal excretion of urobilinogen is increased.[138] Further studies of urobilinogen excretion by modern methods are needed to confirm this observation. If hemolysis is a factor, it is unlikely that it occurs in the pneumonic lung, as once thought, since the jaundice usually appears during the stage of gray hepatization when most of the red cells have vanished,[138] and since jaundice may occur in the absence of pneumonia, as in pneumococcal peritonitis.[9] The fact that the right lung usually is involved in cases with jaundice has led to the impression that a mechanical or anatomic factor may also be involved.[148] This hypothesis has no sound physiologic or pathologic basis and should be abandoned.

The factors that predispose to jaundice are not known. The severity and the extent of the pneumonia do not appear to be crucial, nor does the presence of bacteremia.[186] Since the jaundice occurs late in the course of the disease, it might be anticipated that delayed or ineffectual treatment would be a factor. However, the introduction of modern an biotic therapy does not appear to have duced the incidence of jaundice materially. Suggestive evidence has been presented show that Type II[46] and Type V[142] pneun coccal infections are particularly likely produce jaundice, an effect attributed to severity of the infection in the case of former and to the unusual hemolytic prop ties of the organism in the latter. Unfor nately, the data presented do not permit a conclusions regarding the validity of th interpretations. The antecedent status of liver may be an important factor. This is s gested by the observation that chronic al holics with penumonia are particularly lik to develop jaundice.[186]

The clinical features of the jaundice pneumococcal pneumonia are not distinct The onset is usually on the fifth or the si day of the disease but may occur as early the second or as late as the twelfth day Usually, it is associated with bilirubin and the excretion of large amounts of u bilinogen. In most cases the hepatitis is r to moderate in intensity and subs promptly as the pneumonia resolves. Rar however, it may be sufficiently severe to p duce coma.[24] At one time the occurrenc jaundice was regarded as a bad omen,[93] the results of recent studies do not bear out.[46, 148, 186]

The principal pathlogic changes in the l observed at autopsy include basophilic generation of the hepatic cells, evidence active hepatocellular regeneration with quent mitotic figures, and leukocytic infi tion of the portal triads.[9] The latter is inconstant finding, according to some pat ogists.[138]

STREPTOCOCCUS

Hemolytic streptococcal infections o sionally are complicated by jaundice. N instances occur in association with ba remia,[88] but a few have been reported fol ing scarlet fever.[22] The incidence appear be somewhat lower than in pneumococca fection, jaundice having been encountere less than 3 per cent of cases in one serie 246 streptococcal bacteremias.[88] Jaun may occur also in anaerobic streptoc sepsis,[28] but this is unusual.

In contrast with the relatively minor changes produced by the pneumococcus in cases of jaundice, streptococcal infections are capable of inflicting serious injury on the liver. Two types of hepatic lesion have been described.[107] The first, presumably due to a circulating toxin, is characterized by centrilobular hepatocellular degeneration and necrosis, and an acute polymorphonuclear inflammatory reaction in the portal zones. The other, due to invasion of the parenchyma by histologically demonstrable streptococci, usually consists of scattered focal areas of acute nonsuppurative hepatocellular necrosis. In rare instances the process may be diffuse and resemble acute yellow atrophy. Occasionally, the lesions are zonal in distribution but, in contrast with the toxic type, tend to be periportal[107] or midzonal.[125]

Of interest is the question whether streptococci, borne to the liver either by the blood during episodes of transient bacteremia or by the lymph, are capable of provoking a chronic hepatitis. Once it was believed that many cases of cirrhosis were due to such infections, since streptococci could occasionally be demonstrated in the liver.[125, 121] However, the presence of bacteria is now regarded as a complication of cirrhosis and not its cause. Normally, the liver is capable of clearing the blood of large numbers of bacteria without becoming infected[15] and is sterile on culture.[146] The diseased liver may be less efficient in this respect and thus permit organisms to gain a foothold. It is of interest in this connection to note that the intravenous injection of streptococci in normal animals has no effect on the liver, but when accompanied by a small dose of a hepatotoxin, such as chloroform, produces severe hepatic necrosis.[125]

Streptococci that gain access to the liver via the bile ducts or their lymphatics are said to give rise to a type of chronic hepatitis that terminates in cirrhosis.[107] However, it is difficult to exclude the possibility that the cirrhosis in such cases is secondary to chronic cholangitis.

A curious syndrome, known as cholangitis lenta, has been described as a primary *Streptococcus viridans* infection of the hepatic bile radicles. Clinically, it is characterized by protracted chills and fever, bacteremia, cachexia and anemia. Since jaundice and hepatomegaly are inconstant findings, the hepatic origin of the sepsis may be overlooked. Splenomegaly and ascites are rare. Superficially at least, the syndrome resembles endocarditis lenta (subacute bacterial endocarditis), which accounts for its name. Considerable doubt has been cast on the specificity of the disease, since it has been shown that other bacteria are capable of producing the same clinical picture, and that in carefully investigated cases an underlying stone or malignancy can often be demonstrated in the biliary tract.[59, 97] However, the possibility of a primary *Streptococcus viridans* cholangitis cannot be excluded with certainty, although it must be rare if it occurs at all.

STAPHYLOCOCCUS

The liver is seldom involved in staphylococcal bacteremia, although rare instances of hepatic abscess[159] and jaundice[23,159] have been reported. Unfortunately, the findings in the liver have not been described, so that the pathogenesis of the jaundice in such cases is not known. Although toxic hepatitis would appear to be the most likely cause, it has been suggested that, since marked anemia often accompanies the jaundice, hemolysis may be a factor.[159] The demonstration of methemoglobin in the urine of one reported case[23] would appear to be consistent with this interpretation.

GONOCOCCUS

Jaundice is a relatively frequent finding in gonococcal septicemia due to acute endocarditis[25, 100, 162, 180] and usually is associated with areas of focal necrosis and polymorphonuclear infiltration in the liver.[25, 100] It is not known whether the lesions are due to toxemia or to bacterial invasion. However, the occasional occurrence of hepatic abscess in such cases[10] suggests that bacterial invasion is possible. It is reasonable to suppose that the jaundice is due to hepatocellular injury, although histologic changes have not been demonstrable in all cases.[162] The rapid development of severe anemia and evidence of active phagocytosis of erythrocytes in the reticuloendothelial system in some individuals[100] suggest that hemolysis may be a contributory factor.

At one time hepatitis was a relatively common complication of nonbacteremic gonorrhea.[132] In retrospect, it is reasonably certain that the disease encountered was due to the accidental syringe-transmission of the hepatitis virus.

Occasionally, the gonococcus is responsible for an acute perihepatitis in women with pelvic inflammatory disease.[52, 69] Characteristically, there is a history of gonorrheal infection in the past, and a recent episode, usually within 1 to 2 months, of lower abdominal pain, fever and leukorrhea. The onset is sudden with severe right upper quadrant pain, followed by fever, local tenderness and spasm, and leukocytosis. The pain is aggravated by respiration, coughing and twisting and may radiate to the back or either shoulder. A friction rub is usually audible over the liver. Not infrequently the disease is mistaken for acute cholecystitis, especially since x-ray studies may reveal a nonfunctioning gallbladder, so that often surgical exploration is undertaken. At operation the characteristic findings are a sharply localized dry peritonitis overlying the liver, and an acute inflammatory reaction in the hepatic capsule. Gonococci can usually be recovered from the fluid drained from the area postoperatively. Ordinarily, the symptoms subside spontaneously within a few days to a week. In many cases the acute inflammatory reaction is followed by the development of "violin-string" adhesions between the anterior surface of the liver and the abdominal wall. As a rule, these are asymptomatic but occasionally give rise to chronic or intermittent pain.

ESCHERICHIA COLI

The jaundice, which occasionally complicates *E. coli* bacteremia, is said to be the result of increased hemolysis and hepatocellular injury.[87] However, no descriptions of the hepatic lesions are available, and no direct evidence of in-vivo hemolysis has been presented, so that the pathogenesis of the jaundice must be regarded as uncertain. In experimental animals intravenously injected cultures of *E. coli* have no effect on the liver, unless accompanied by a small dose of an hepatotoxin, such as chloroform.[125]

Of interest is the occurrence of *E. coli* septicemia as a complication in Laennec's cirrhosis,[177] suggesting either that the abil
of the liver to engulf and destroy organis
coming to it from the intestinal tract is i
paired, or that the development of an ext
sive collateral circulation permits organis
to circumvent the phagocytic action of
liver.

SALMONELLA

Two types of hepatitis are seen in asso
tion with salmonella infections: one t
occurs in epidemics and is due to a conc
rent infection with the hepatitis virus,
the other that occurs sporadically and is
rectly related to the effects of the salmone

From time to time outbreaks of jaund
occur in which members of the salmon
group can be recovered from the blood
feces.[13, 73, 178] During World War I, w
these were especially prevalent among tro
in the Dardanelles and Mesopotamia, it
not certain whether the jaundice was du
a salmonella cholangitis[13, 73, 178] or t
double infection with both the salmonella
the virus of infectious hepatitis.[112] Howe
it is now evident that, under condition
crowding and poor sanitation, epidemic
both diseases can occur simultaneously,
that double infections probably account
most cases of jaundice associated with
monella infections. This was beautifully d
onstrated under experimental condition
Havens and Wenner,[66] who observed 2
stances of *Salmonella choleraesuis* b
remia in a group of 5 individuals
experimentally induced viral hepatitis l
in an institution where salmonella infect
were prevalent. In most outbreaks of h
titis complicated by salmonellosis, mem
of the paratyphoid group (*S. paratyphi*
S. schottmülleri) have been implicated
the Dardanelles and Mesopotamian
paigns previously mentioned, jaundice
curred in 5 per cent of infections with
organisms.[179]

Occasionally, the jaundice that ac
panies a salmonella infection is c
unrelated to an intercurrent viral hepatit
paratyphoid fever, for example, it ma
the result of an acute suppurative cholan
while in food poisoning with *S. typhim*
and *S. enteritidis* it usually is due to a
hepatitis.[179] On clinical grounds alone it

be very difficult to distinguish between these various types of jaundice. However, viral hepatitis should be suspected when jaundice occurs with great frequency during an epidemic of paratyphoid, and particularly when cases of jaundice begin to appear in individuals without evidence of salmonella infection. Suppurative cholangitis is more likely to be the cause in sporadic cases of paratyphoid. Toxic hepatitis is almost always responsible when jaundice occurs in food poisoning.

TYPHOID

Hepatomegaly occurs in approximately 25 per cent of patients with typhoid fever.[167] It usually appears during the second or the third week of the disease and persists until defervescence. The enlargement is probably related to the presence of the characteristic focal areas of parenchymal necrosis and the portal inflammatory reaction found at autopsy.[108] Occlusion of the sinusoids by proliferation and embolization of endothelial phagocytes[108] and toxic injury[58] have been cited as possible etiologic factors in their pathogenesis. Similar lesions have been produced in experimental animals with an antigenic extract of typhoid bacilli,[122] so that a toxic origin is highly probable.

Jaundice is said to be a relatively rare complication in typhoid fever.[126] However, in one large series it occurred in almost 4 per cent of the cases.[167] Usually, it appears at the height of the fever, runs a relatively benign course and is associated with many of the clinical features of viral hepatitis.[179] Although it usually is presumed to be due to a mild cholangitis,[126, 179] there is little or no autopsy evidence to support this. A few instances of suppurative cholangitis, pylephlebitis and solitary hepatic abscess have been reported,[126] but the nature of the lesion in most mild cases is not known. A toxic hepatitis would appear to be the most likely etiology in cases without suppuration of the biliary tract,[167] but morphologic studies are too few in number to warrant any definite conclusions.

Acute cholecystitis occurs in a small proportion of individuals with typhoid fever and may be a serious complication if suppuration ensues. It probably occurs more often than is recognized clinically[167] and, as is well known, may serve to initiate a chronic cholecystitis and cholelithiasis. Such individuals are particularly likely to become carriers of typhoid bacilli.

SHIGELLA

As in the case of salmonella infections, epidemic bacillary dysentery occasionally is accompanied by a high incidence of jaundice,[169] a complication not seen in sporadic cases. On epidemiologic grounds it is highly probable that the coincidence of jaundice and dysentery in such epidemics is due to double infections with shigella and the hepatitis virus. Acute cholangitis has been considered as a possible cause of the jaundice, but this appears to be unlikely, since the lesion has not been observed in autopsy studies.

CLOSTRIDIA

Patients with *Cl. welchii* (*perfringens*) bacteremia develop an intense jaundice and severe anemia due to the hemolytic action of the exotoxin produced. The serum often contains free hemoglobin, methemoglobin and hematin,* in addition to increased amounts of bilirubin.[23] Although the jaundice is primarily of hemolytic origin, hepatic injury is often a factor, since the organisms tend to invade the liver and give rise to extensive gas formation.

The other clostridia involved in gas bacillus infections produce similar hemolytic exotoxins and are capable of inducing jaundice in the same manner.

The relationship of clostridial infections to infarction of the liver is of interest, since hepatic artery ligation is being advocated as a therapeutic measure in the management of esophageal bleeding due to cirrhosis and portal hypertension. In dogs, it has been found that occlusion of the arterial circulation to the liver is invariably fatal within 96 hours. This effect is due to the development of clostridial bacteremia and massive hepatic necrosis and can be prevented by the administration of large doses of penicillin or chlortetracycline.[34, 111] Apparently the reduction in oxygen tension permits the rapid growth of anaerobes in the liver, leading to bacteremia and massive hepatic necrosis. Although massive hepatic necrosis and death may follow hepatic artery ligation in man,[19, 80] clostridial infections do not appear to be responsible. This species difference is probably related to the fact that clostridia are normally present in the dog's liver[34, 146] but not in man's.[146]

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* More recent studies suggest that the principal pigments are free hemoglobin, methemalbumin and bilirubin.

TUBERCULOSIS

Judging from the results of autopsy studies[103, 143, 172] and tests of hepatic function[72] it is evident that the liver is frequently injured during the course of tuberculous infection. In general, two types of lesion are seen: (1) granulomatous reactions clearly due to hematogenous spread of tubercle bacilli from extrahepatic sites via the hepatic artery or portal veins, and (2) nonspecific changes in the hepatic parenchyma and stroma, such as fatty infiltration, fibrosis, amyloidosis and passive congestion, apparently related to the effects of prolonged infection, malnutrition, anoxia and cardiac failure.

Although hepatic tuberculosis is always secondary to disease in other tissues and seldom produces significant symptoms, the liver occasionally bears the brunt of the infection, giving rise to striking clinical manifestations that may suggest primary hepatic involvement. In all instances, however, an extrahepatic focus can be demonstrated, although it is often relatively insignificant.

Types of Lesions. The types of tuberculous lesions encountered in the liver include the following:

1. Miliary tubercles associated with
   A. Chronic tuberculosis
   B. Acute miliary tuberculosis
   C. Pylephlebogenous tuberculosis
   D. Splenic tuberculosis
2. Conglomerate tubercles
   A. Tuberculomas
   B. Tuberculous cholangitis

It should be emphasized that the basic lesion, a discrete miliary tubercle, is identical in all types, and that differences in morphology and symptomatology merely reflect variations in the number and the distribution of these lesions. Characteristically, the hepatic tubercle is just visible to the naked eye. Early,
it comprises a closely packed mass of e
thelioid cells, which later are surrounded a
infiltrated by a few lymphocytes. As
lesion matures, it grows in size, giant c
appear, peripheral lymphocytosis and fibr
occur, and small areas of central eosinoph
necrosis become evident. Ultimately, it m
be replaced by fibrous tissue. Frank cas
tion is unusual, except when a number
tubercles coalesce. There is nothing char
teristic about the distribution of the lesio
some being located in the parenchyma, oth
in the portal triads. Acid-fast bacilli
surprisingly difficult to demonstrate
tologically. In one large autopsy series,
example, they were found in only 37.9
cent of the hepatic granulomata examined
and even fewer have been demonstrate
specimens of tissue obtained by needle
opsy.[92, 109] This is an important point, si
in the absence of acid-fast bacilli and ca
tion, it is impossible to distinguish betw
the lesions of tuberculosis and a variet
other granulomatous diseases.[92]

Chronic Tuberculosis. Discrete mi
granulomata are demonstrable in the liv
a high proportion of fatal cases of chr
tuberculosis. The incidence may be as
as 99 per cent[103] and is seldom less tha
per cent.[145, 172] Their occurrence has
correlated with the presence of intes
lesions in some autopsy series[103] but n
others,[145] indicating that tubercle bacilli
reach the liver either by way of the p
vein or the hepatic artery. Although th
indicative of a terminal disseminatio
many instances, recent experience wit
opsy material suggests that similar h
togenous spread to the liver can be de
strated at all stages of the disease.[92, 1
one series of 13 cases with active tub
losis, needle biopsy revealed hepatic g
lomata in 2 patients with predominantly
monary disease, and in 1 with os
disease.[92] Suggestive evidence also has
presented[173] to show that there may
correlation between the number, the lo
distribution and the histologic features
lesions, and the clinical course of the u
lying disease. The hepatic lesions in
group seldom produce symptoms or s
cant alterations in function. However
jaundice is said to occur in 80 per c

patients with chronic tuberculosis and the terminal type of dissemination.[176]

Acute Miliary Tuberculosis. The liver is almost always heavily seeded with tubercles in acute miliary tuberculosis, and occasionally these give rise to jaundice and hepatomegaly.[45, 87, 92, 109, 176] It is not known whether the jaundice in such cases is due to granulomatous destruction of the parenchyma, obstruction of intrahepatic bile ducts, or toxic hepatocellular injury. Possibly, multiple mechanisms are involved.

Needle biopsy of the liver has proved to be a useful diagnostic procedure in miliary tuberculosis. Characteristic granulomata can be demonstrated in almost all cases, and sometimes even before pulmonary lesions are detectable radiographically.[38, 43, 92, 109] However, caution must be exercised in interpreting such lesions as conclusive evidence of tuberculosis, unless acid-fast bacilli can be demonstrated, which is not always possible.[92, 109] Nevertheless, taken together with the presenting clinical features, the finding of miliary granulomata is often all that is needed to confirm a tentative diagnosis in cases of obscure fever.

Pylephlebogenous Tuberculosis. Rarely, there is massive dissemination of tubercles to the liver via the portal vein from an abdominal focus, without significant involvement of other tissues.[134, 176, 182] The principal clinical manifestations are chills, fever, prostration and progressive hepatomegaly, accompanied occasionally by jaundice[176] and splenomegaly.[134] Death usually ensues within a few weeks.

Splenic Tuberculosis.[71, 181] Miliary tubercles are found in the spleen in most cases of acute disseminated tuberculosis and, less commonly, in association with other forms of the disease. Rarely, tuberculosis appears to be "primary" in the spleen, although it is obvious that the infection must have arisen in an undetected healed focus elsewhere in the body. Nevertheless, in the early stages of the disease the lesions appear to be confined to the spleen. Later, they spread to other tissues and especially the liver, by way of the portal vein. Acute and chronic forms of "primary" splenic tuberculosis are recognized and are characterized clinically by marked splenomegaly and signs of hypersplenism. Splenectomy is alleged to be curative in such cases.[181]

Tuberculomas. Rarely, large caseating masses or abscesses of tuberculous origin are found in the liver. A primary lesion is usually demonstrable in the intestine, the mesenteric nodes or the lungs, but occasionally none can be found.[67] It has been suggested that, in contrast with miliary granulomata of hematogenous origin, large caseating lesions are the result of a lymphogenous spread. This appears unlikely in view of the fact that the lymphatic drainage of the liver is from within outward. The lesions are either single or multiple and produce chills, fever, enlargement and tenderness of the liver and, less commonly, splenomegaly[8] and jaundice.[123] Death usually ensues within a few months, although recovery has been reported following surgical drainage.[67]

Tuberculous Cholangitis (Tubular Tuberculosis of the Liver). The rarest type of hepatic tuberculosis involves the intrahepatic bile ducts and is said to occur chiefly in children and in races peculiarly susceptible to tuberculous infection.[143] The disease is due always to rupture of a caseating tuberculoma or abscess into the biliary tract and never to an ascending infection. However, tuberculous lesions can be found in the intestine or adjacent mesenteric nodes in most cases.[143, 176] The lesions may be limited to one area or may follow along the course of the ducts. Clinically, the principal manifestations are a septic temperature, pain in the right upper quadrant, and cachexia. Jaundice and clay-colored stools occur when large ducts are involved[176] but are not seen in all cases.[143] The course is rapidly downhill and usually terminates fatally within a few months.

Nonspecific Changes in the Liver. The liver is fatty in a high proportion of individuals who die of tuberculosis, the incidence ranging between 34 and 42 per cent in most autopsy series.[82, 103, 145, 172] It is said to be somewhat higher in cases of tuberculous enteritis,[82] but this has not been borne out in all studies.[145] At the present time there appears to be little doubt that malnutrition is largely responsible for this change. It is the most common cause of hepatomegaly in tuberculosis and probably accounts for many of the minor alterations in hepatic function encountered.

Cirrhosis is found in from 1 to 6 per cent of fatal cases.[103, 145, 172] It represents a coincidental lesion in some instances but is probably due to malnutrition in most. Healing of granulomata results in focal fibrosis but does not produce frank cirrhosis.

At autopsy many livers exhibit portal fibrosis, lymphocytosis, and proliferation of bile ducts,[103, 145] changes apparently unrelated to the presence of tubercles. The significance of these lesions is uncertain, although it has been suggested, on insufficient evidence, that they are due to the toxic products of the tubercle bacillus.[145] Possibly they represent an early stage of nutritional cirrhosis in some instances and healed granulomatous lesions in others.

Amyloidosis is far less common than fatty liver, occurring in only 5 to 10 per cent of fatal cases of pulmonary and osseous tuberculosis.[82, 172] The amyloid is deposited between the sinusoidal endothelium and the parenchymal cells and causes atrophy of the latter as it increases in amount. Clinically, the liver is enlarged and firm when the amyloidosis is extensive and often is accompanied by splenomegaly. Despite the loss of parenchymal cells, there is remarkably little impairment of hepatic function. Jaundice is so rare that, when it occurs, it is almost always due to some other cause. Albuminuria, indicative of renal involvement is present in some but not all cases. Ascites occurs occasionally but seldom is due to hepatic failure, hypoalbuminemia, renal failure, cardiac decompensation and tuberculous peritonitis being the more common causes. (See also Chap. 25, Amyloidosis.)

Several authors[103, 172] have commented on the frequency of passive congestion of the liver in fatal cases of tuberculosis. In one series[172] it was present in 94 per cent of the cases and was attributed to right-sided heart failure secondary to advanced pulmonary disease. This would appear to be a reasonable interpretation, although other possible factors have not been excluded.

Liver Function in Tuberculosis. Many patients with active tuberculosis exhibit minor abnormalities of liver function.[73] These are of a nonspecific nature and do not serve to
distinguish between the various types
patic lesions described. Moreover, so
flect alterations in the serum protein
related to infection and are not due to
tural changes in the liver. Characteris
there is a fall in serum albumin and a
alpha- and gamma-globulin concentrat
The prothrombin level is depressed
sionally and may be a contributory fa
the pathogenesis of hemoptysis.[99]

LEPROSY

Approximately half the cases of
matous leprosy that come to autopsy
miliary granulomata in the liver.[128, 170]
cannot be distinguished from the lesion
in sarcoidosis and other granulomato
eases. The liver also often contains a

BRUCELLOSIS

Biopsy studies[161] indicate that
granulomata occur with great regula
cases of active brucellosis. In addition
livers show portal fibrosis and lympho
and necrosis of occasional parenchyma
The granulomatous lesions, which are
posed of masses of epithelioid cells.
few lymphocytes, giant cells and plasm
closely resemble those seen in sarc
tuberculosis and other granulomato
eases.[92] Caseation does not occur, b
types of necrosis are seen occasionally
tical lesions have been observed in m
guinea pigs infected with *Br. abor*
evidence has been presented to sh
the proliferation of epithelioid cells.
are derived from the Kupffer cells, is
tion to the intracellular growth of or
and is a sign of a good defense mech
Animals infected with the more inva
suis develop suppurative lesions, wh
has been interpreted as evidence of
sistance. It is of interest, in this con
to note that all the hepatic granulom
onstrated by needle biopsy have occ
patients with *Br. abortus* infections.[92]
patic lesions are said not to occur in
infections with *Br. suis* and
However, there may be exceptions,
cated by a recent report of acute
with jaundice in a well-documented
brucellosis due to *Br. suis*.[124]

e hepatic granulomata of brucellosis
ly are associated with few clinical mani-
ions. although hepatomegaly is very
non.[39] Several instances of jaundice have
reported,[39, 126] but these are unusual.
ic function is impaired only slightly
may be normal even in the presence of
erous lesions.[130]

e of the more perplexing problems in
llosis is the question of whether it ever
rise to cirrhosis. The occasional associ-
of the two diseases in the same individ-
has been interpreted variously as evi-
e that brucellosis is a direct cause of
osis,[134] an important contributory fac-
or a purely coincidental infection.[115]
e present time, it cannot be said that the
ence implicating the brucella as a direct
e of cirrhosis is wholly convincing. Al-
gh periportal fibrosis accompanies the
lopment of hepatic granulomata in bru-
sis, it is by no means certain that it is
rerunner of cirrhosis, especially since
ic granulomata have not been observed
e cases of cirrhosis reported.[39, 49, 116,]
[134] Theoretically, healing of widely dis-
nated granulomata might lead to a
e fibrosis that simulates cirrhosis. How-
in animals it has been shown that heal-
is not accompanied by scarring.[27] The
that the morphologic picture is usually
of Laennec's cirrhosis and appears late
e disease following a prolonged period
ebility suggests that the cirrhosis may be
d on a nutritional deficiency, as in
rculosis.

TULAREMIA

uring its dissemination, *B. tularense* fre-
tly invades the liver, among other
ns, and produces characteristic focal
ns.[54] In one autopsy series,[104] these
e present in 10 out of 12 cases. The acute
ns, which are seen during the first 2
ks of the disease, are characterized by
s of focal necrosis infiltrated with large
onuclear cells. Later, they become gran-
natous and exhibit a central zone of
osis, which is occasionally caseous, sur-
nded by radially arranged epithelioid cells
fibroblasts and a peripheral collar of
phocytes and giant cells.[54]
linical manifestations of hepatic involvement are unusual. In one series, signs of overt hepatitis were evident in only 4 out of 600 cases.[32] However, a somewhat higher incidence has been observed in fatal cases, which invariably are associated with a disseminated infection.[132] Jaundice and hepatosplenomegaly are the usual findings and occasionally are associated with peritonitis and ascites.[52]

GRANULOMA INGUINALE

Occasionally, the Donovan body, now believed to be a gram-negative bacillus, produces a disseminated infection which involves the joints, the bones and the viscera. The liver in such cases may be studded with miliary abscesses filled with foamy mononuclear cells containing Donovan bodies.[136]

LEPTOSPIROSIS (WEIL'S DISEASE)

Definition. Leptospirae that are pathogenic for man characteristically invade the blood stream and produce an acute febrile illness of relatively brief duration. Some of the more virulent strains also induce acute inflammatory lesions, especially in the liver, the kidneys, the meninges, the muscles and the eyes, which not only prolong the disease but also give rise to some of its most striking clinical manifestations.

The term Weil's disease is somewhat ambiguous, since it is used both as a general designation for any type of leptospirosis that produces jaundice, and as a synonym for infections with *L. icterohaemorrhagiae* specifically. The former interpretation is undesirable, since a classification of the leptospiroses based on the presence or the absence of jaundice overemphasizes the importance of an inconstant secondary manifestation of a systemic disease and necessitates an arbitrary distinction between icteric and nonicteric infections with the same organism. However, the latter interpretation is no easier to defend, since several strains of leptospirae are capable of producing the same clinical picture first described by Weil. The term leptospirosis, qualified wherever possible by the strain and the special tissues involved, would appear to be more informative and less confusing but has the disadvantage of being somewhat more cumbersome.

Often a number of other terms are used to describe infections with special strains of leptospirae. These include canicola fever (*L. canicola*), mud fever (*L. grippotyphosa*), autumnal fever (*L. autumnalis*), swineherd's disease (*L. pomona*) and others. Some of the strains produce jaundice about as frequently as *L. icterohaemorrhagiae*, while others do so only rarely or not at all.

Etiology. A large number of serologically distinct strains of pathogenic leptospirae have been identified,[61, 175] but only 5 have been isolated from human cases in the United States: *L. icterohaemorrhagiae*, *L. canicola*,[140, 141] *L. pomona*,[17, 147, 168] *L. grippotyphosa*[160] and *L. autumnalis*.[56] It is quite possible that others will be recognized as more extensive serologic testing is employed.

Most leptospiral infections in this country are due to *L. icterohaemorrhagiae*, and a smaller number to *L. canicola*, strains that often produce jaundice. *L. grippotyphosa*, recently recovered from a jaundiced case in Texas,[160] has been recognized for some time as the cause of mud fever or summer influenza, a mild nonicteric illness common in Eastern Europe.[175] *L. autumnalis* has been identified as the etiologic agent in Fort Bragg fever, a mild febrile disease characterized by fever, splenomegaly and pretibial rash without jaundice.[56] In Japan the same organism, or a closely allied variant, produces autumnal fever, a mild illness frequently accompanied by jaundice. *L. pomona* has been implicated in several nonicteric infections in this country.[17, 147, 168] In Europe, it produces swineherd's disease, which is characterized by a biphasic fever, rash, meningitis and gastroenteritis, and occasionally by jaundice.[60]

Although the various strains of leptospirae differ in antigenic structure and virulence, they exhibit identical morphologic features. Characteristically, they are long slender structures, measuring 6 to 9 μ in length and 0.25 μ in breadth, with sharp pointed ends that are hooked either in the same or opposite directions. Tightly coiled minute spirals running their length give them a beaded appearance under darkfield illumination. Despite the absence of flagellae or undulating membranes, they are capable of a variety of undulating, twisting and propulsive movements. Apparently, minute forms occur, s
Berkefeld filtrates, which contain no vis
leptospirae, are capable of infecting gu
pigs.[76] In liquid media leptospirae are d
onstrated best by means of darkfield illu
nation. Although it is possible to stain th
in dried thick films by the Giemsa tech
silver stains are required for their demons
tion in tissues.

Leptospirae may be cultivated at a t
perature of 25 to 30° C. in a variety of m
containing guinea-pig kidney, whole bloo
serum, and may be grown on the ch
allantoic membrane of the chick emb
However, it is more common to propa
them in susceptible animals. Young gu
pigs are used most widely, but since
may be resistant to such strains as *L. ca*
ola[140] and *L. grippotyphosa*,[160] ham
and white mice often are employed. A
variety of other rodents are also suscep
to experimental infections.

Coincidental with the disappearanc
organisms from the blood stream in le
spiral infections, there is a rapid rise in
titer of specific serum agglutinins. Alth
cross-agglutination with other leptospir
common, the titer usually is signific
higher with the specific strain invo
Therefore, serologic tests are reasonabl
liable in distinguishing between various l
spiral infections, although it is still not
tain that all the strains identified in this
are distinct species. For the most acc
identification of leptospiral strains, ab
tion and neutralization tests are us
needed.

Epidemiology. Human infections
leptospirae are invariably the conseq
of close contact with animals or their ex
The animals that constitute the natura
ervoir of these infections do not neces
suffer any ill effects from the organism
harbor, as in the case of the rat. How
some species, such as the dog, devel
acute illness which may closely resembl
seen in man.

As the principal vector of *L. icteroha*
rhagiae, the rat is responsible for most
of Weil's disease. The dog is also capa
transmitting the disease to man but d
only infrequently.[117, 119] *Leptospirae*
haemorrhagiae also have been rec

m a variety of other animals, including l mice, cats, pigs, horses and foxes and ters,[7, 21] but these do not appear to be re-nsible for infections in man.

In the rat, the leptospirae are found in the ney and the urine, but not in the blood, liver or other tissues.[75] The infection is nsmitted from rat to rat by ingestion of ne-contaminated food and water, and pos-ly through sexual intercourse.[21] A high portion of the rat population has been nd infected in all parts of the world where rveys have been carried out.[75, 150] In the ited States the incidence in urban areas ries from 25 to 35 per cent.[117, 119] Con-dering the opportunities for infection, it is teworthy that only 67 cases of Weil's dis-se were reported in this country up until 41,[7] an incidence well below that of Hol-nd and England where rat leptospirosis is more common. No doubt this reflects a ilure on our part to recognize the disease. his is borne out by the rapid increase in the umber of cases reported during the past 10 ars, since clinicians have become aware the prevalence of the disease, and diag-stic laboratory facilities have become more nerally available. Reports of 20 to 80 cases om a single city have become common-ace,[64, 120] and there is reason to believe at this trend will continue as interest in the sease grows, and public health authori-es provide more facilities for serologic sting.

With few exceptions, human infections ith *L. icterohaemorrhagiae* can be traced to ntact with contaminated rat urine. Occa-onally, the disease is acquired as a result of t-bite,[75] accidental contact with live cul-res in the laboratory[150] or handling of in-cted rat tissues, as in the case of ratcatchers. an-to-man and intra-uterine fetal infections e said to occur rarely,[7] and at least one in-ance of probable venereal transmission has een reported.[150] The abraded skin and the tact mucous membranes, especially of the njunctival sac, the nose, the mouth and the roat, serve as the usual portals of entry. here is considerable doubt that leptospirae n penetrate the intact skin,[150] and it is un-kely that they gain entry through the stom-ch and the upper intestinal tract, since they e readily destroyed in an acid medium. However, the guinea pig can be infected by feeding leptospirae or by instilling them into the rectum.[76]

Although Weil's disease may be acquired in any rat-infested environment, certain occupations provide peculiarly favorable conditions for infection, so much so, indeed, that some states now recognize leptospirosis as a compensable occupational disease.[21] In this country, fish cutters and cleaners, butchers, miners, ratcatchers, sewer workers, plumbers, tunnel diggers, garbage handlers and dock workers are particularly subject to the disease.[7, 21, 120] As might be expected, infected dogs constitute a special hazard for veterinarians and other dog handlers.[117] In other parts of the world, especially in tropical and semitropical areas, the disease is particularly likely to affect sugar-cane cutters[130] and rice-field workers who are obliged to work in contaminated irrigated fields. During warfare soldiers not infrequently become infected in poorly drained trenches.

Another important way in which Weil's disease may be acquired is by swimming or by accidental immersion in stagnant bodies of water. The latter is particularly common in the canals of Holland.[175] Although swimming is said to be somewhat less hazardous than accidental immersion, outbreaks have been reported among swimmers both in this country[65] and abroad.[139, 175]

The environmental factors that favor the transmission of Weil's disease and account for many of its epidemiologic features include dampness, a temperature of 22° to 25° C., and a neutral or slightly alkaline medium[75] in which leptospirae may survive for as long as 3 weeks.[21] Although most cases in this country are said to occur during the summer months,[7] in one very large series reported from Detroit[120] no seasonal variation in incidence was observed. In view of the occupations that predispose to infection, it is not surprising to find that 90 per cent of the cases occur in adult males, and that the disease is relatively rare in children.[120]

L. canicola infections follow close contact with dogs or their excreta.[140, 141] On the basis of serum agglutinin studies in healthy animals, it would appear that the incidence of leptospirosis is high, varying from 4 to 34 per cent in different areas.[117, 140] The relative frequency of *L. canicola* and *L. icterohaemorrhagiae* infections in dogs varies, but in general the former greatly outnumber the latter.[117] Both strains produce a severe illness in the dog which terminates fatally in from 50 to 80 per cent of cases. The disease may be manifested by jaundice, a severe hemorrhagic gastroenteritis, or both.[140] Following recovery, the animal may excrete leptospirae in the urine for a number of months, apparently due to the development of a chronic nephritis. Since *L. canicola* survives in neutral stagnant water, as in the case of *L. icterohaemorrhagiae,* human infections occasionally may follow bathing in contaminated water. More often, however, they are the consequence of other types of direct or indirect contact with urine. The relative infrequency of *L. canicola* infections in man, despite a high incidence in dogs, has been attributed to the following: (1) the dog is only a temporary shedder of leptospirae; (2) it seldom contaminates the environment to the same extent as the rat; and (3) its urine is acid, which does not permit long survival of leptospirae.[140]

In the swampy areas of eastern Europe, *L. grippotyphosa* is carried by the vole and the wood mouse, which contaminate the soil and the water with their urine and thus transmit the infection to man. The only case reported in this country[160] occurred in a Texas farmer in whom the source of infection was not determined.

The animal vector of the *L. autumnalis* strain responsible for Fort Bragg fever is not known.[56] However, the closely related type strain *Akiyami A,* which produces autumnal fever in Japan, is carried by the field mouse.[175]

In some parts of Europe, swine are asymptomatic carriers of *L. pomona* and serve as the intermediate host in swineherd's disease.[60] In this country, the same organism is responsible for recurrent iridocyclitis in horses and recently has been identified in cattle,[57] swine[147] and mules.[147] Of the cases reported in this country, one outbreak occurred in a group of individuals who swam in a creek in which several dead hogs had been seen,[147] one followed the handling of raw beef and pork in an abattoir,[17] and the last occurred in an individual who had be in contact with young pigs.[168] Since *pomona* has not been found in rats,[147] it highly probable that the infection in th individuals was acquired from swine.

Pathogenesis. Following an incubat period of 7 to 13 days (extreme 4 to 19) and coincidental with the onset of sympto *L. icterohaemorrhagiae* which have gai access to the body make their appearanc the blood in large numbers and soon are seminated to many, if not all, of the tissue By the end of a week, however, the le spirae usually have vanished from the bl and seldom can be found in any of the sues except the kidney and occasionally liver.[64, 76, 116] Rarely, a few degenerate le spirae may be demonstrable in the adren the lymph nodes, the myocardium, spleen, the testis, the lung, the pancreas, intestine, the gallbladder, the central ner system and the skin as late as the sixte day of the disease.[76] It is generally assu that the disappearance of organisms f both the blood and the tissues is related to development of immune bodies,[76] altho diagnostically significant titers usually ca be demonstrated until several days to a w later.

Clinical manifestations related to the volvement of the liver, the kidney and o special tissues do not become evident the end of the first week, or even later, w leptospiremia is diminishing or actually ceased. Since most fatalities occur in the ond and the third week of the diseas little is known about the early lesions in However, the autopsy findings in se cases that have died on the fifth or the day[64, 116, 156] suggest that tissue injury occur during the stage of leptospiremia before localizing symptoms become evi Of interest in this connection is the obs tion that, in experimental animals, l spirae may be demonstrable in the live fore they appear in the blood.[6]

The liver, the kidneys, the muscles the blood vessels are the tissues most quently involved in leptospirosis *icteroh orrhagiae,* but many others may be af in individual cases.

LIVER. One of the striking featur

Weil's disease is the remarkable discrepancy between the severity of the jaundice and the extent of the hepatic lesions found at autopsy. The histologic changes observed usually include: (1) dissociation of the hepatic cells and disorganization of the centrilobular architecture, (2) active hepatocellular regeneration, as evidenced by the presence of binucleate cells and mitoses, (3) minimal degenerative changes in the cytoplasm and the nuclei of the parenchymal cells, (4) bile stasis, especially in the centrilobular canaliculi, and (5) a predominantly mononuclear infiltration of the portal zones.[7, 47, 116, 156] In the most severe cases, small areas of focal necrosis occur, and, rarely, massive hepatic necrosis has been reported.[158] However, it should be emphasized that necrosis is distinctly unusual, and that the liver actually may show no changes whatever in severe cases with deep jaundice.[156] It is difficult to account for the unusual regenerative activity of the parenchyma which is such a striking feature in this disease. It would seem reasonable to suppose that it represents a response to antecedent cellular necrosis. However, serial studies of the liver in experimentally infected animals do not support this interpretation, mitotic activity being demonstrable in the absence of necrosis, as in man.[6] Leptospirae can be demonstrated in the liver in only half the cases that come to autopsy. They are usually found overlying the parenchyma cells but do not appear to penetrate them.[6]

The jaundice in Weil's disease is almost certainly due to hepatocellular injury. Since it may occur in the absence of histologically demonstrable cellular changes,[156] it must be assumed that morphologically intact cells suffer a functional impairment of bilirubin excretion. There is no evidence of extrahepatic biliary obstruction, and the presence of bile thrombi in the canaliculi is probably the consequence of cellular injury and bile stasis, rather than of intrahepatic biliary obstruction. Phagocytosis of erythrocytes occurs in the liver, the spleen and the sites of hemorrhage,[6] so that an increased rate of hemoglobin breakdown may contribute to the development of jaundice. However, it is never of sufficient severity to account for the depth of jaundice usually encountered in Weil's disease.

Since nonicteric leptospirosis is rarely fatal, it is not known whether it produces changes in the liver. Abnormalities of hepatic function have been observed in some cases[141] but not in others.[89]

KIDNEYS. In general the renal lesions in Weil's disease[7, 47, 79, 156] are more impressive than those in the liver, and leptospirae are demonstrable more frequently. When present, the latter are found both in the tubules and the interstitial tissue.[7, 64]

The kidneys usually are enlarged and moderately bile-stained. Microscopically they show: (1) degeneration and necrosis of the convoluted tubules; (2) a diffuse inflammatory reaction in the interstitial tissue characterized by an infiltrate of lymphocytes, monocytes and occasional polymorphonuclear and eosinophilic leukocytes; (3) numerous granular casts, and cellular debris in the distal convoluted and collecting tubules; and (4) small hemorrhages into the capsule, the interstitial tissue and the tubules. The glomeruli are usually intact but occasionally show changes resembling those in acute glomerular nephritis.[7]

The lesions in the kidney are almost certainly due to the invasion of leptospirae and not to the associated hepatic failure. As might be expected from their localization, they frequently produce a type of renal insufficiency that closely resembles that seen in lower nephron nephrosis due to other causes.

MUSCLES. Highly characteristic lesions can be demonstrated in the skeletal muscles in most *L. icterohaemorrhagiae* infections, and their number can be correlated with the severity of the disease.[157] It is quite possible that they are responsible for the myalgia which is such a striking clinical feature. Early in the disease individual fibers show localized areas of vacuolization with loss of striations and multiplication of adjacent sarcolemma nuclei. Later, sarcolemma cells invade these necrotic foci and remove any remaining debris. In mild cases, new myofibrils appear within these cells, while in more severe cases the foci are infiltrated with lymphocytes and plasma cells and undergo fibrosis. Leptospirae have not been demonstrated in any of these lesions, although they have not been studied before the eighth day of the disease. The absence of hemorrhage and vascular lesions serves to distinguish them from Zenker's degeneration and the lesions seen in rickettsial disease.

BLOOD VESSELS. The serosal surfaces, the mucous membranes and many of the viscera frequently exhibit petechial hemorrhages. In more severe cases, there may be purpura of the skin and gross bleeding into the gastro-intestinal tract, the pulmonary tree or the urinary tract. Since there is no reduction in the platelet count or prolongation of the bleeding and coagulation time, it is generally believed that the hemorrhages are due to capillary injury.[7] The prothrombin concentration is usually only slightly to moderately decreased,[153] but it occasionally falls to very low levels in severely jaundiced cases[21] and thus may contribute to the hemorrhagic tendency.

CENTRAL NERVOUS SYSTEM.[7] The meninges are often the site of a low-grade lymphocytic and plasmocytic inflammatory reaction. This usually is accompanied by pleocytosis of the cerebrospinal fluid. Degenerative changes are seen in the neurons, but there is no inflammatory reaction in the substance of the brain or the spinal cord.

HEART. A variety of lesions may occur in the heart. These include (1) hemorrhages into the epicardium and the endocardium, (2) round-cell infiltration and degenerative changes in the myocardium resembling those seen in skeletal muscle[21] and (3) rarely, acute vegetative endocarditis.[7]

Clinical Manifestations.[7, 79, 153] The clinical manifestations of leptospirosis *icterohaemorrhagiae* emerge in two phases. Early in the disease, there are severe constitutional systems related to the presence of leptospirae in the blood. Later, localizing signs appear pointing to invasion of the specialized tissues, especially the liver, the kidneys and the meninges. The two phases overlap to some extent, and in some cases localizing signs never develop. In classical Weil's disease, hepatic and renal manifestations dominate the latter half of the clinical course. Occasionally, these are accompanied by signs of an inflammatory reaction in the
meninges, the eyes, the myocardium or o
tissues. Although these are generally c
sidered as complications of the disease,
are, in fact, evidence of the same typ
leptospiral invasion that occurs in the
and the kidney. Occasionally, the live
spared, and the major localizing manif
tions are limited to other specialized tiss
This is particularly likely to occur in
infections with *L. icterohaemorrhagiae*
with some of the other strains that ordin
do not induce jaundice.

Characteristically, the onset of sympt
in leptospirosis *icterohaemorrhagiae* is
den, with fever, muscular pain, headache
severe prostration. The lumbar muscles
the calves are particularly involved, and
be tender. Chilly sensations are common
occasionally a shaking chill ushers in
disease. Marked conjunctival injectio
usually present and is a helpful diagn
sign. As the disease progresses, hemorr
herpes labialis, gastro-intestinal symp
nuchal rigidity and cough often appear.
billiform and scarlatiniform rashes are
occasionally but are unusual. At this
leptospirae can be demonstrated in
blood, but physical signs, other than
of a severe infection, may be comp
lacking. Leukocytosis is the rule, an
cerebrospinal fluid often contains a
creased number of cells.

Toward the end of the first week,
leptospirae are disappearing from the
the temperature falls, but the patient's
eral condition usually worsens. Alt
muscular aching and many of the othe
stitutional symptoms diminish, prost
anorexia and gastro-intestinal com
increase, and, at the same time, the c
teristic signs of hepatic and renal in
ment make their appearance. Jaundice,
usually is noted on the sixth or the s
day, rapidly increases in intensity, re
a peak within a few days. Generally it
companied by enlargement and tender
the liver, bilirubinuria and, occasiona
clay-colored stools, pruritus and brady
Splenomegaly is unusual, occurring
than 10 per cent of cases. During the
febrile period, the urine often cont
small amount of albumin, a few ce

ts. However, as the typical renal lesion velops, the urinary output falls, albumiria increases, casts, leukocytes and erythrotes appear in increasing numbers, the ecific gravity tends to become fixed at 010, and, in the most severe cases, azomia and anuria ensue. The blood pressure nds to fall to a low level, and a number of her cardiovascular abnormalities may be ted. Epistaxis and other hemorrhagic phemena often occur at this time. Central rvous system manifestations are also very mmon, especially in seriously ill patients.

In favorable cases, signs of clinical imovement become evident as early as the d of the second week. Convalescence may delayed until the third or fourth week severe infections. Recovery is usually slow, nvalescence being marked by asthenia and emia. Relapses are relatively common, curring in approximately 20 per cent of ses. These are characterized by a brief crudescence of fever and mild constituonal symptoms which appear between the ird and the fifth weeks. Rarely, there are veral such episodes.

Most deaths occur between the ninth and e sixteenth days, although fatalities have een reported as early as the fifth and as late the twenty-first day.[116] Renal and hepatic ilure account for most of these, but cardiac ecompensation, massive hemorrhage and rminal pneumonia may be important comlicating factors. The mortality rate in *L. terohaemorrhagiae* infections varies in diferent parts of the world. Differences in strain irulence, individual susceptibility and enironmental factors probably account for ome of these variations, but the frequency ith which mild infections are recognized ould appear to be an important factor, espeially since the mortality rate in nonicteric ases is negligible. In this country the rate is pproximately 25 per cent, which is somehat higher than in parts of Europe where here is a greater awareness of the disease.[150]

Fever. Characteristically, the temperature ises abruptly to 102° to 104° F., runs an regular remittent course and falls to normal y rapid lysis in 4 to 7 days. Occasionally, he duration of fever is more prolonged, but rarely exceeds 12 days.[47, 74] Although a sudden onset is highly characteristic, it is not seen in all cases.[68] Severe shaking chills are relatively uncommon. The brevity of the fever and the absence of recurrent chills are of great importance in differential diagnosis.

Jaundice. The onset of jaundice is variable but rarely if ever occurs before the third or after the tenth day of disease. Characteristically, it reaches a maximum within a few days and then subsides over a period of a week to 10 days. The intensity of the jaundice is variable, depending on the severity of the infection but, in general, tends to be mild to moderate.[68] Tests of liver function usually reveal the typical pattern of hepatocellular injury.[35, 164] On the basis of current statistics, it is estimated that one third of the infections with *L. icterohaemorrhagiae* are unaccompanied by jaundice.[21] It has been suggested that the liver is not completely spared in such cases, since they often exhibit hepatomegaly[153] and impairment of liver function.[141]

Renal Manifestations. All gradations of renal injury are seen in Weil's disease. In approximately 15 per cent of cases, the kidney appears to be spared.[175] This is particularly apt to occur in patients without jaundice. However, severe renal failure has been reported in nonicteric Weil's disease and has been termed leptospiral nephritis.[165] Despite its severity, the renal lesion appears to be reversible and goes on to complete recovery in nonfatal cases. Leptospirae often can be demonstrated in the urine between the thirteenth and fifteenth days and occasionally as early as the sixth day.[76] Usually they disappear by the fortieth day but, rarely, may persist for many months.[165]

Meninges and Central Nervous System. Spinal-fluid pleocytosis and xanthochromia are seen in approximately 90 per cent of patients with Weil's disease.[32] The cell count is usually under 100 but may be as high as 3,000 per cu. mm. Lymphocytes predominate, but in the first week of the disease as many as 50 per cent of the cells may be polymorphonuclear. The nature of the pigment is not known. Although it is assumed to be bilirubin, there is usually a discrepancy between the small amount that can be determined chemically and the depth of the color observed visually.[37] The protein content is increased in only half the fluids with pleocytosis and is seldom high. Only half the cases with abnormal spinal fluid findings develop clinical signs of meningitis. Occasionally, meningismus occurs in the absence of spinal fluid abnormalities. Leptospirae may be demonstrable in the fluid during the first week of the disease.[79]

Meningitis is seen also in nonicteric infections with *L. icterohaemorrhagiae*[16, 30] and may be readily confused with other forms of lymphocytic meningitis due to neurotropic viruses. Certain clinical and epidemiologic features suggest that there may be some fundamental differences between this type of leptospiral meningitis and that in classical Weil's disease. The former occurs in males under the age of 30, chiefly late in the summer, and usually is associated with a normal leukocyte count and little or no muscle tenderness.[16] It is particularly apt to occur following bathing or accidental immersion in infected waters and often is accompanied by pharyngitis, suggesting that the portal of entry may be in the nasopharynx or possibly the conjunctivae.[30] Characteristically, the clinical course is benign, and the patients are rarely severely ill. An identical type of meningitis is seen frequently in swineherd's disease due to *L. pomona*.[60]

A variety of other central nervous system manifestations occur in seriously ill patients with leptospirosis. These include delirium, hallucinations, restlessness, apathy, convulsions and loss of consciousness. Since morphologic changes seldom can be demonstrated, it must be assumed that they are due to functional disturbances related to the toxemia of infection, renal insufficiency and hepatic failure.

HEMORRHAGE. Epistaxis and small conjunctival petechiae are relatively common in Weil's disease. In severe cases, hemorrhages occur with great regularity.[47, 74] These may take the form of purpura in the skin and the mucous membranes, melena, hematemesis, hemoptysis or hematuria. Rarely, massive hemorrhage into the adrenals may produce the Waterhouse-Friderichsen syndrome.[78]

OCULAR MANIFESTATIONS. Iridocyclitis is a late sequel of Weil's disease, which occurs
in approximately 10 per cent of patients.
may appear during convalescence or not u
a number of months have elapsed follow
recovery. The same complication has b
reported recently following an *L. pom*
infection in this country.[17] Optic neuritis
hemorrhages into various portions of
ocular globe also occur but are unusual.

GASTRO-INTESTINAL SYMPTOMS. A
rexia, nausea, vomiting, constipation and
dominal pain are frequent complaints
Weil's disease. The pain is of partic
importance, since it may lead to error
diagnosis and needless surgical explora
for acute appendicitis or cholecystitis.[68]

CARDIOVASCULAR MANIFESTATIONS.
addition to hypotension and tachycar
which are common in many other severe
fections, patients with Weil's disease are
ticularly subject to disturbances in car
function. Dilatation of the heart, ga
rhythm, conduction defects, arrhythmias
electrocardiographic abnormalities are
known to occur.[21] These probably ca
related to the presence of myocardial les
although functional disturbances due to
failure, hemorrhage and toxemia must p
role in many cases. Pericarditis also o
occasionally.[37] All of these abnormalitie
pear to be reversible and leave no resi
following recovery. Rarely, leptospira
responsible for an acute vegetative e
carditis.[7] Of interest is a recent repo
myocarditis and arthritis due to ar
pomona infection which simulated rheu
fever.[168]

RESPIRATORY. Almost half the pa
with Weil's disease develop cough and
tum, and occasionally these are accomp
by signs of a patchy pneumonitis.[21, 153]

CANICOLA FEVER. Infections with *L.*
ola produce a clinical picture that is a
identical with that of classical Weil's d
due to *L. icterohaemorrhagiae*. Howeve
symptoms tend to be somewhat less s
jaundice is less frequent, and dea
rare.[140, 141]

Laboratory Features. HEMATOLOG
[139, 153] The leukocyte count usually r
between 12,000 and 20,000 but may
high as 30,000 per cu. mm. The perc
of polymorphonuclear cells is increase

ccasionally myelocytes can be demonstrated the peripheral blood smear. The bleeding nd clotting times and the platelet count are sually normal. A microcytic hypochromic nemia, probably due to hemorrhage, is often resent late in the disease.

LIVER-FUNCTION TESTS. In jaundiced ases the results of liver-function tests are onsistent with hepatocellular injury. There s usually an increase in serum bilirubin, hymol turbidity, serum alkaline phospha-ase, bromsulphalein retention and urine uro-ilinogen, and a decrease in prothrombin nd serum cholesterol. The cephalin-choles-erol flocculation reaction is positive.[35] Bile s present in the urine, and the stools are ccasionally clay-colored.[153] The prompt irect-reacting fraction of bilirubin in the erum is increased.[164] On electrophoretic nalysis, the serum shows an increase in lpha-2 and gamma globulin and a decrease n albumin.[164]

DEMONSTRATION OF LEPTOSPIRAE. Lepto-pirae are present in the blood during the irst week of the disease but not thereafter. They usually appear in the urine toward the nd of the second week and may persist for 30 days or more.[76] Occasionally, they can be lemonstrated in the spinal fluid during the eriod of leptospiremia.[79]

Three methods are used for detecting eptospirae in these fluids: (1) darkfield examination, (2) animal inoculation and (3) culture. On the whole, the inoculation of susceptible animals, especially young guinea pigs, mice and hamsters, is most satisfactory. Cultural technics are probably equally effective, but few routine laboratories are prepared to carry them out. Darkfield examination of blood is the least reliable method, except in the hands of an expert, since fibrin strands are readily mistaken for leptospirae. However, the procedure may be of value, in demonstrating leptospirae in the urine.

Guinea pigs, weighing approximately 175 Gm., are injected intraperitoneally with 3 to 5 ml. of defibrinated blood or plasma, or the spun sediment of freshly passed neutral urine suspended in saline. The animal usually exhibits jaundice on the seventh or the eighth day and dies between the tenth and the twelfth. At autopsy, the characteristic findings are bile staining of the tissues, and hemorrhages into the pleura and the peritoneum. Leptospirae are readily demonstrable in the blood and the peritoneal fluids by darkfield examination or culture. It is often possible to recover the organisms earlier by examining aspirated peritoneal fluid when the animal's temperature rises on the fourth or the fifth day.

SEROLOGIC TESTS. Specific agglutinins appear in the serum during the second week. Rarely, they can be detected as early as the sixth day,[79] but diagnostic titers of 1:300 usually are not found before the fourteenth day.[7] The titer continues to rise during convalescence, often exceeding 1:20,000, and not infrequently remains elevated for many years.[127] The most reliable results are obtained with a freshly prepared antigen of suspended formalinized leptospirae.[150]

Specific lysins and complement-fixing antibodies are also present in the serum but are less important diagnostically.

Diagnosis. During the first few days, Weil's disease may be confused with a number of febrile illnesses, including influenza, typhus, trichinosis, brucellosis and sepsis of various types. As localizing signs develop in the liver, the kidneys and the meninges, it must be differentiated from viral hepatitis, obstructive jaundice, acute nephritis and acute bacterial and viral meningitis.

The occupational history, or other opportunity for exposure to a rat-contaminated environment or to dogs, the abrupt onset, early prostration, muscle pain and prominent conjunctival injection should alert the clinician to the possibility of Weil's disease early in the course. Later, the combination of jaundice with signs of nephritis and/or meningitis is highly suggestive of the diagnosis. Spinal-fluid xanthochromia and pleocytosis are particularly important clues, since the combination is seldom seen in any type of jaundice other than leptospiral. In severe viral hepatitis and decompensated cirrhosis with jaundice, the spinal fluid often contains a small amount of bilirubin and an increased concentration of protein, but the cell count remains normal.[4] Rarely, biliary obstruction is associated with spinal-fluid xanthochromia, but only when the jaundice is intense and of long duration. In contrast, Weil's disease often produces xanthochromia when the jaundice is mild and of very short duration.[32] The brevity of the febrile period, usually under a week and rarely as long as 12 days, is another important feature which serves to distinguish Weil's disease from many of the other conditions which simulate it.

The most difficult cases to recognize are those in which jaundice does not develop. These may present as acute fevers without localizing signs, or as cases of primary meningitis or nephritis. Except in the very mildest infections, the clinical features are identical with those of the leptospiremic stage of Weil's disease.

Of prime importance in the diagnosis is the need for a more general awareness of the wide distribution of the disease and its protean manifestations. Once Weil's disease is considered as a possibility, laboratory confirmation is relatively simple. During the first week an attempt should be made to isolate leptospirae from the blood by guinea-pig inoculation. At the same time, a specimen of blood should be examined for leptospiral agglutinins. Since these usually are not demonstrable in significant titer until the end of the second week, the first determination merely serves as a baseline for subsequent determinations, which should be carried out at weekly intervals. A titer of 1:300 is generally considered diagnostic. If there is no rise in titer by the end of a month, the diagnosis of Weil's disease can be excluded. Muscle biopsy and spinal-fluid examination are important adjuncts, since they make it possible in many cases to establish a presumptive diagnosis before the results of guinea-pig inoculation can be obtained, or before the rise in agglutinins can be demonstrated.

Treatment. Of all the specific therapeutic agents that have been tried in Weil's disease, only immune serum of animal origin[7, 76, 139] and transfusions of convalescent whole blood and plasma[7, 68, 76, 130] have proved to be effective and then only if given before the appearance of jaundice. Unfortunately, antileptospiral serum is not available in this country, and, only under the most unusual circumstances, is a convalescent donor at hand.

The results of antibiotic therapy have been equivocal and are still under investigati
Penicillin is lethal for leptospirae in cultu
and protects guinea pigs against death
given within 18 hours of infection; howe
it is completely ineffective if administe
following the appearance of symptor
There are reports of excellent results in
tients treated on the first day of diseas
and failures in cases whose treatment
begun after the appearance of jaundic
In a group of 67 cases recently studie
Puerto Rico, penicillin, chlortetracyc
oxytetracycline, chloramphenicol and st
tomycin had no effect on the duratior
fever and failed to prevent or ameliorate
patic and renal involvement.[63] Of sp
interest was the observation that the
biotics frequently failed to eradicate le
spiremia and prevent relapses.[184] It sh
be noted, however, that the treatment
not begun until an average of 6.7 days
elapsed, and that 44 per cent of the
were jaundiced. In view of its in-vitro a
on leptospirae and its effectiveness in
tecting animals against fatal infection
would seem reasonable to employ ma
doses of penicillin early in the cours
Weil's disease, at least until such time a
results of antibiotic therapy have been e
ated more fully.

The general management of Weil's di
is very much like that of any other acut
temic infection. However, there is, in
tion, an urgent need for a close wat
kidney function, and, when renal in
ciency supervenes, for judicious regulat
fluid, electrolyte and nitrogen balance.
other types of acute renal failure char
ized by severe oliguria and azotemia, th
is to establish and maintain the in
chemical environment as close to norn
possible. This is accomplished by li
the intake of fluid and electrolytes to
ured or estimated losses and maintai
low-protein intake while providing su
carbohydrate and fat to meet calor
mands. Frequent determinations of
and urine electrolytes greatly facilitat
regulation but are not always essential.
loss is often an important considerat
severe infections and should be re
There is no evidence that the diet h
influence on the hepatic lesion in lept

is, and the high-protein intake often recommended in liver disease may be distinctly harmful if renal insufficiency is present.

Prophylaxis. Vaccines prepared from heat-killed or phenol-treated leptospirae are effective immunizing agents.[175] They are used o some extent in areas where the disease is prevalent, as in Japan, and in laboratory workers who are heavily exposed to infection.

SPIROCHETAL AND PROTOZOAN INFECTIONS

Relapsing Fever. The liver and the spleen often are enlarged in relapsing fever and, in severe cases, may be associated with jaundice.[36, 183] The latter is not accompanied by other signs of hepatic failure and fades promptly when the fever subsides. Presumably, the jaundice is due to hepatocellular injury, although, as in the case of Weil's disease, necrosis is unusual. In fatal infections, which invariably are accompanied by jaundice, the liver is enlarged and intensely congested. The Kupffer cells are swollen and contain phagocytized red blood cells, spirochetes and pigment, and the portal zones show a moderate inflammatory reaction.[5]

Malaria. Judging from the results of liver function studies,[70, 91, 118, 149] *naturally acquired* malaria appears to produce a mild form of hepatic injury rather frequently. However, not all of the functional disturbances observed can be attributed to the direct effects of the plasmodium; nor are they all necessarily indicative of hepatocellular damage. Bromsulphalein retention, for example, which occurs with great regularity at the height of an attack, has been shown to be due, in part at least, to the nonspecific effects of fever,[106] while the increase in serum bilirubin and urine urobilinogen, which frequently are accompanied by a significant fall in hemoglobin,[70] are in a large measure the result of increased hemolysis. Characteristically, the serum albumin level tends to fall, while the globulin level rises. This is particularly striking in *therapeutic* malaria, when the patient is permitted to experience a number of paroxysms of fever before therapy is instituted.[95, 96] A sharp fall in serum cholesterol, especially in the esterified fraction, is also seen in these cases.[62, 96] It is reasonable to suppose that the changes in serum protein and lipid are the consequence of impaired hepatic function, although other factors may be contributory. The cephalin-cholesterol flocculation reaction is almost invariably strongly positive,[135] even in attacks of relatively brief duration.[101] Since it occurs with regularity and often is unaccompanied by other signs of hepatic involvement, it has been suggested that flocculation may be due to nonspecific changes in the serum proteins related to infection, rather than to hepatocellular injury.[135] Alterations in galactose tolerance and hippuric acid synthesis have also been observed in some cases.[101] Characteristically, hepatic function promptly returns to normal following recovery from an attack of malaria, although occasionally minor abnormalities persist for many weeks.[101] However, even repeated relapses do not lead to any permanent impairment of function.[101, 171]

Hepatomegaly can be demonstrated some time during an acute attack in approximately half the cases of malaria.[91] It is almost invariably accompanied by splenomegaly and occasionally it is associated with tenderness. Following recovery, the liver usually returns to its normal size within a few days. However, after repeated relapses it may remain enlarged for a long time.[171] Clinically detectable jaundice is unusual, occurring in less than 1 per cent of cases and, when present, is usually mild.[70, 91] It appears on about the fourth day of illness and usually lasts for about a week. Only half the cases are associated with hepatomegaly. There appear to be two distinct types of jaundice: one, very mild, and almost certainly hemolytic in origin; the other, somewhat more severe and probably due to a combination of hemolysis and hepatocellular damage. The former is characterized by a slight elevation in total serum bilirubin, without a concomitant increase in the prompt direct fraction, or the presence of bile in the urine. In the latter both the direct and the indirect fractions of serum bilirubin are increased, and the urine contains both bile and increased amounts of urobilinogen. *Plasmodium falciparum* infections are particularly likely to produce jaundice, while quartan malaria rarely does so.[70]

Studies of liver biopsy material obtained during acute attacks of malaria have revealed a number of interesting histologic changes.[42] These include: (1) swelling of the parenchymal cells with alterations in cytoplasmic staining, (2) a marked increase in hepatocellular mitotic activity, with hyperchromatism and variability in the size of the nuclei, (3) compression of the sinusoids, and infiltration with lymphocytes and monocytes, (4) occasional small foci of necrosis and (5) hyperplasia of the Kupffer cells. At autopsy, cases of chronic malaria show hemosiderosis of the parenchymal cells, infiltration of the Kupffer cells with hemozoin pigment, and centrilobular atrophy and necrosis.[70, 91, 166] Not infrequently there is also a diffuse fibrosis of the liver, which is generally regarded as an unrelated complication of malaria.[166] Of interest is the occasional occurrence of nonspecific hepatic granulomas, which have been described by at least two groups of workers.[42] Their significance and pathogenesis are not known.

The type of liver damage seen in *therapeutic* malaria differs from that in the *naturally acquired* disease in that it tends to be more severe, is occasionally fatal[114] and often occurs late in the disease or even following recovery.[33, 96] There are two reasons for these differences: (1) in many cases the hepatic lesions are due to an intercurrent infection with the hepatitis virus acquired during the inoculation of malarial blood,[33] and (2) the course of the malaria is not interrupted by therapy until the patient has had a large number of paroxysms. In both instances the hepatic injury produced tends to be more severe than in naturally acquired malaria. This is well illustrated in the case of the serum albumin concentration, which almost invariably falls to a low level in inoculation malaria and often is accompanied by edema,[95] rare features in the naturally acquired disease.

Toxoplasmosis. The infantile form of toxoplasmosis, an infection presumably acquired in utero from a mother without overt signs of the disease, characteristically produces encephalomyelitis, hydrocephalus and chorioretinitis and runs a fatal course. Almost half the cases develop hepatomegaly and jaundice, but morphologic changes in the liver are rare.[31] Only one of the 18 cases reported up to 1946 exhibited significant
patic lesions (severe parenchymatous de
eration, distortion of the lobular architec
and extramedullary hematopoiesis), an
only one other were toxoplasma demon
ble in the liver. Therefore, no satisfac
explanation can be offered for either
hepatomegaly or the jaundice. In a few
stances, jaundice has been associated
the presence of nucleated red blood cel
the peripheral blood and splenomegaly,
ing to a clinical diagnosis of erythroblas
fetalis. However, it is generally believed
both the hematologic changes and the j
dice are related in some way to the ur
lying infection.[31]

A small number of acute toxoplasma i
tions have been reported in adults.
These have been characterized clinical
fever, rash and signs of encephalitis
pneumonitis. All have terminated fatall
shown lesions in the myocardium, the
the liver, the spleen and the brain. Gen
the liver has exhibited focal areas of in
mation with or without necrosis. How
in one case with moderate impairme
function during the course of the diseas
significant lesions were found in the liv
autopsy.[85]

MYCOTIC INFECTIONS

ACTINOMYCOSIS[41]

The liver is the commonest solid ab
nal viscus attacked by actinomycosis.
ally the organisms reach the liver by w
the portal vein from an infected focus
appendix, the cecum, the colon or the re
However, infection may occur also by
extension from contiguous viscera, or b
of the hepatic artery during generalize
semination. Occasionally, the disease a
to be primary in the liver, although it
vious that it must have originated
inconspicuous lesion somewhere in th
tribution of the portal vein. There are
rare instances in which the gallbladd
pears to be the primary focus. It ha
suggested that the organisms in such
may invade the gallbladder by way
biliary tract.

On reaching the liver *Actinomyce*

luce a granulomatous reaction and fibrosis. the lesions extend, they undergo central crosis, giving rise to characteristic thick- lled multiloculated abscesses. These often ach the surface of the liver and may extend to the abdominal wall, the diaphragm or e adjacent viscera.

The signs of hepatic involvement may be erlooked when there are more extensive sions in the other intra-abdominal viscera. sually, however, the liver is enlarged and nder and may exhibit localized swellings its surface. Irregular fever, sweats, leuko- tosis and anemia are the usual concomi- nt findings.

Diagnosis depends on the demonstration *Actinomyces bovis* in aspirated pus or tis- e sections. Until the organisms are found, ifferentiation from amebic abscess, malig- ancy and gumma may be difficult.

BLASTOMYCOSIS

The primary lesion in *Blastomyces der- iatitidis* infections is either in the skin or ie lungs. In the pulmonary type, general dis- emination is not uncommon, and the liver one of the organs frequently involved.[113] he lesions produced are usually suppurative ut occasionally are granulomatous and losely resemble those in tuberculosis.

Brazilian blastomycosis,[29] a closely re- ated disease due to *Paracoccidioides brasili- nsis,* usually starts in the mouth and spreads the adajacent lymph nodes. In some cases he organisms are disseminated to the liver, he spleen and the bone marrow. The prin- ipal clinical manifestations, which include ever, anemia, eosinophilia, adenopathy and plenomegaly, often suggest Hodgkin's dis- ase. In the liver the organisms are localized hiefly in the periportal tissues, where they ncite a granulomatous reaction character- zed by a nodular infiltration of lymphocytes, osinophiles and foreign-body giant cells. ater, these areas undergo fibrosis, giving ise to a cirrhosislike picture.

COCCIDIOMYCOSIS

Coccidioides immitis gives rise to two ypes of infection: (1) an acute benign, self- imited, influenzalike disease, known as "San oaquin Valley Fever," and (2) a chronic progressive coccidial granulomatosis which is often fatal. The former represents a primary infection of the lung and often is associated with hilar adenopathy and erythema nodosum. The latter is the result of a widespread dissemination of the organisms from a primary site, usually in the lung, to many of the tissues including the liver, where they produce isolated granulomas and abscesslike foci.[151]

HISTOPLASMOSIS

There is growing evidence that histoplasmosis is a relatively common disease in this country, especially in the Mississippi Valley.[14] Most infections are asymptomatic and are manifested by benign pulmonary lesions or skin sensitivity to histoplasmin. Occasionally, however, *Histoplasma capsulatum* gives rise to serious lung disease, ulcerative lesions in the mucosa of the oropharynx and the larynx, or widely disseminated lesions in the liver, the spleen, the visceral lymph nodes, the bone marrow, the kidneys, the adrenals, the endocardium and other tissues.[129] The characteristic lesion produced is a granuloma composed of epithelioid and giant cells. The organisms, which are present in large numbers engulfed in epithelioid and other phagocytic reticuloendothelial cells, may be difficult to demonstrate in routine sections, unless stained by the Hotchkiss-McManus technic.[77, 131] The close resemblance between the clinical and the histologic features in histoplasmosis and sarcoidosis has been emphasized repeatedly.[77, 131, 136] Even the Schaumann bodies and the asteroids, so characteristic of the lesion in sarcoidosis, may be seen in histoplasmosis.[131] Differentiation between the two diseases depends upon the presence or the absence of histoplasma in the tissues and skin sensitivity to histoplasmin. On clinical grounds, histoplasmosis should be suspected when ulcerative lesions are found in the oropharynx and the larynx, or when there is extensive involvement of the adrenals. In many instances death is due to adrenal insufficiency.[181] Not infrequently the central portions of the granuloma undergo caseation necrosis, in which case the disease may be mistaken for tuberculosis.[129]

Hepatomegaly and splenomegaly occur in more than half the cases with the disseminated form of the disease.[129] As a rule, these give rise to no localizing symptoms, but occasionally they are accompanied by jaundice and ascites. Fever, anemia and weight loss are the more usual associated symptoms.

Since the liver is involved frequently, needle biopsy should be of considerable value in establishing the diagnosis of histoplasmosis, especially when more superficial lesions are not available for histologic study. However, it must be recognized that the lesions of histoplasmosis cannot be distinguished from those of sarcoidosis, tuberculosis and other granulomatous diseases on histologic grounds alone,[92] so that a careful search for organisms in appropriately stained sections, and a histoplasmin skin test are indicated whenever hepatic granulomata are encountered.

Moniliasis and Aspergillosis

Small abscesses are found occasionally in the liver in cases of disseminated moniliasis[137] and aspergillosis.[44] Although they may produce jaundice, they are often silent, the principal clinical manifestation being related to the involvement of the lungs, the heart valves and the central nervous system. The number of disseminated *Candida* infections appears to be increasing, apparently due to the widespread use of antibiotics, which encourage the growth of these organisms.[94] Drug addicts, who use the intravenous route, are also peculiarly susceptible.[81, 187]

DISEASES OF PRESUMED INFECTIOUS ORIGIN

Infectious Mononucleosis

Histologic evidence[2, 12, 84, 86, 174, 185] confirms the impression gained from functional studies that the liver is almost invariably involved in infectious mononucleosis. The outstanding morphologic feature is an intense inflammatory reaction involving the portal triads and sinusoids. Various types of mononuclear cells, including lymphocytes, large monocytes, epithelioid cells and plasma cells, predominate, but a few polymorphonuclear cells and eosinophils are seen in some cases. In addition, there is proliferation and swelling of the Kupffer cells in the sinu
where, in conjunction with other mon
cells, they tend to form small aggr
which resemble granulomata. One of t
teresting features of the lesion is the a
complete absence of hepatocellular ne
in the face of striking evidence of reg
tive activity. Variations in the size
staining properties of the hepatic
mitotic figures and hyperchromatic
cleate cells are common. A few cells
minor cytoplasmic changes, including
larity, vacuolization and increased e
philic staining, suggestive of early deg
tion. The focal aggregates of Kupffe
and monocytes occasionally produce
sure atrophy and eosinophilic necro
adjacent parenchymal cells. In jau
cases it is not unusual to find sma
thrombi in the canaliculi and bile pigm
the hepatic cells. Occasionally, the reti
fibers are thickened, but fibrosis do
occur.[84] The bile ducts show no sign
changes. Almost identical focal inflamm
lesions have been described in the
nodes, the bone marrow, the kidney
heart, the lungs, the testes, the adrena
the brain,[2] so that the hepatic lesions in
tious mononucleosis probably repre
local manifestation of a generalized re
endothelial and monocytic response, a
a specific inflammatory reaction involv
parenchymal cells.

The results of liver-function tests a
normal in most, if not all, cases of inf
mononucleosis.[28, 40, 48, 50, 55, 83] Howe
is not certain that these are indica
hepatocellular injury in all instances. T
that they are not closely correlated w
histologic changes in the liver,[84, 174] a
fact that they often remain abnorm
after recovery[18, 48, 83] suggest that s
the abnormalities, such as the ce
cholesterol flocculation and thymol tu
reactions, may be due to nonspecific
protein changes related to the underl
fection. Characteristically, the serum a
level falls, while the gamma globulin
Occasionally, there is also a less-prom
increase in alpha-1 and beta globul
though the heterophile agglutinins ar
chiefly in the gamma-globulin fracti
do not appear to be responsible for

ted electrophoretic pattern.[163] Strongly sitive cephalin-cholesterol flocculation re- tions and increased thymol turbidity occur at least 80 per cent of cases, the number pending on the frequency with which the ts are repeated. Bromsulphalein retention, creases in serum alkaline phosphatase and inary urobilinogen, and decreases in serum olesterol esters and prothrombin are less nstant findings. The serum bilirubin level increased in 10 to 30 per cent of cases.[18, 4] Bilirubinuria is said to occur in the ab- nce of hyperbilirubinemia,[40] an observation at still needs to be confirmed.

Clinical manifestations of liver disease are latively uncommon. Jaundice occurs in 5 10 per cent of cases,[1, 18, 55, 83] and hepato- egaly slightly more frequently.[20] In general, e jaundice tends to be mild and subsides in ss than a month. However, in occasional stances it is intense and persists for several onths.[1] The appearance of jaundice may recede or coincide with the onset of lympha- enopathy, and occasionally occurs without mphadenopathy. There is usually little diffi- ulty in recognizing that the jaundice is due hepatocellular injury; however, the differ- ntiation from viral hepatitis may be ex- eedingly difficult, especially since atypical mphocytosis may occur in both diseases. he diagnosis depends on the demonstration f a significant rise in the heterophile agglu- nin titer, which usually occurs in the second eek; rarely, the rise does not occur until e seventh or the eighth week.[11] The results f liver function tests are usually consistent ith some type of hepatocellular injury but exceptional cases[83] may suggest an ob- tructive jaundice.

The clinical significance of the morpho- gic and the functional changes in the liver nonicteric cases is still a matter of dispute. ome authors[40] take the extreme view that ey are responsible for the constitutional ymptoms in infectious mononucleosis, and hat diets high in protein, carbohydrate and itamins hasten recovery. Although there may e a correlation between the degree of hepatic ysfunction and the intensity of the symp- oms, there does not appear to be any con- incing evidence that the two are related ausally. Indeed, it is highly probable that oth reflect the severity of the infection. Most investigators[48] have failed to confirm the alleged effectiveness of dietotherapy in shortening the course of the disease.

The results of liver function tests usually return to normal by the end of the second month.[48, 83] Occasionally, however, abnormalities may persist for as long as 2 years,[18] which has led to concern over the possibility that chronic hepatitis and cirrhosis may follow an attack of infectious mononucleosis. One alleged case of postinfectional cirrhosis has been reported,[98] but chronic alcoholism and malnutrition were present and could not be excluded as the responsible etiologic factors. In the opinion of most investigators[28, 86] there is no convincing histologic or clinical evidence that infectious mononucleosis gives rise to any type of chronic liver disease. However, it is quite possible that premature ambulation in patients with significant liver damage may prolong convalescence and aggravate postinfectional asthenia. For that reason, it would seem reasonable to enforce bed rest, at least until jaundice and hepatic tenderness have subsided. Persistent abnormalities in cephalin-cholesterol flocculation and thymol turbidity, unaccompanied by other signs of active liver disease, are not an indication for continued restriction of activity.

SARCOIDOSIS

It has become increasingly evident in recent years that sarcoidosis is almost invariably a generalized disease, even though the clinical manifestations often suggest a very limited distribution of the lesions. Among the tissues involved, the liver stands second only to the lymph nodes and the lungs. In a series of 138 autopsies, collected from the literature,[26] the incidence of hepatic granulomata was no less than 66.5 per cent. Recent studies of needle biopsy material indicate that the incidence is equally high in less severe, nonfatal cases, being approximately 75 per cent in two series totaling 41 cases.[92, 155] Considering the frequency with which granulomata can be demonstrated in such small specimens, it must be concluded that the lesions are usually numerous and uniformly distributed throughout the liver. Occasionally, hepatic granulomata resembling sarcoids are found in individuals without other signs of the disease.[92] Not all of these are due to sarcoidosis, but in many instances a prolonged search discloses confirmatory evidence of the diagnosis. On the basis of collected biopsy reports, it has been estimated that sarcoidosis accounts for approximately 2 per cent of all liver disease.[26] Obviously, this cannot be regarded as an accurate estimate, since it is not based on a randomly selected group of cases, but it does serve to indicate that the disease is not rare.

The characteristic lesion in the liver[92] is a sharply circumscribed, discrete, round or oval compact mass of epithelioid cells, giant cells and a few lymphocytes imbedded in a fine reticulum stroma. It may be found anywhere in the lobule or within a portal zone. Only occasionally do individual lesions coalesce to form conglomerate masses. Minute areas of central fibrinoid necrosis are seen in a few lesions, but caseation does not occur. Schaumann bodies and asteroid inclusions are relatively uncommon. As the lesion matures it usually develops a collagen envelope and ultimately undergoes fibrosis and hyalinization. Rarely, the granulomata, which are usually submiliary in size, coalesce to form large masses which infiltrate the liver diffusely and destroy its normal architecture, giving rise to a cirrhosislike picture.[26, 92] Of considerable importance is the recent observation that the hepatic lesions in sarcoidosis seldom can be differentiated from those of tuberculosis, berylliosis, erythema nodosum and a variety of other granulomatous diseases on histologic grounds alone.[92] Therefore, it is essential to exclude all other known causes before accepting such lesions as evidence of sarcoidosis.

The vast majority of individuals with histologically demonstrable hepatic sarcoidosis exhibited few, if any, overt signs of liver disease. Although hepatomegaly is often present, it is usually only slight to moderate in degree and seldom is associated with tenderness, induration or nodularity. Moreover, hepatic enlargement occasionally is due to cor pulmonale and congestive failure, so that it is not necessarily indicative of the presence of hepatic granulomata. In the occasional case with extensive hepatic involvement, the liver may be greatly enlarged, firm and tender. Splenomegaly occurs in approxi
half the individuals with significant h
megaly and may be due either to gran
tous infiltration, congestion or both.
collateral signs of chronic liver disease
as jaundice, spider nevi, palmar eryt
increased collateral venous circulation
phageal varices, ascites and edema, ar
tively uncommon. A few instances of
dice and ascites have been reported,[26,
the writer has seen one case with
portal hypertension and recurrent bl
from esophageal varices, necessitat
portacaval anastomosis. Many patient
active sarcoidosis have gastro-int
symptoms, but only rarely can these
lated to the involvement of the liver
cally.[92]

Minor alterations in hepatic functi
be demonstrated in a high proportion
dividuals with sarcoidosis.[92] Some of
such as increases in serum bilirubin,
alkaline phosphatase and bromsulpha
tention, appear to be related to the p
of hepatic granulomata, but others, in
an increase in serum globulin, thym
bidity and cephalin-cholesterol flocc
or a fall in serum albumin, may
in part at least, to extrahepatic facto
hyperglobulinemia is closely correlat
the extent and the activity of the lesic
erally and, therefore, is a useful inde
lowing the course of the disease. T
serum alkaline phosphatase levels o
ally seen in sarcoidosis are almost c
due to extensive hepatic involvem
though granulomatous infiltration
bones may play a role in some ca
though the impairment of hepatic
parallels the extent of the lesions in t
it is generally less severe than in cirrh
other types of chronic hepatitis.

Liver disease seldom is suspected
of sarcoidosis with scattered hepati
lomata. However, when the liver is
enlarged, and especially when acco
by splenomegaly, it may be exceedin
cult to differentiate sarcoidosis fron
sis, chronic hepatitis due to other
Hodgkin's disease and other forms c
nant lymphoma.

Needle biopsy of the liver is a pa

able diagnostic procedure in sarcoidosis,
only in cases with overt signs of liver dis-
but also in those with predominantly
hepatic lesions. Since histologic confir-
on is always essential, the procedure may
vide the only means of establishing the
nosis when more accessible lesions in the
and the peripheral lymph nodes are not
lable for examination.

Erythema Nodosum

rythema nodosum is generally regarded
a manifestation of hypersensitivity to a
iety of agents, including bacteria, viruses,
gi and chemical compounds.[51] Occasion-
, the skin lesions, which are the most
king feature of the disease, are accom-
ied by hilar adenopathy, pulmonary in-
rates and eye lesions[90] and recently it has been shown that the liver often contains sarcoidlike miliary granulomata.[92] The significance of such disseminated lesions is not known. They have been interpreted variously as evidence of tuberculous infection, sarcoidosis and a nonspecific response to infection. The writer has been able to demonstrate the presence of hepatic granulomata in several instances of erythema nodosum associated with active tuberculosis and acute streptococcal infections, but not with drug reactions, suggesting that the lesions may represent a nonspecific response to infection. However, too few drug reactions have been studied to exclude the possibility that they too produce granulomata. Recently, Löfgren[102] has presented convincing evidence to show that erythema nodosum and hilar adenopathy often represent the primary manifestations of sarcoidosis.

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Chapter 14

PORTAL CIRRHOSIS (LAENNEC'S CIRRHOSIS)

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GENERAL CONSIDERATIONS

Hepatic cirrhosis is a disease characterized by chronic, diffuse inflammation of the liver, accompanied by proliferation of connective tissue, by degenerative and regenerative changes in liver cells, resulting in distortion of hepatic architecture. Many clinicians and pathologists have regarded cirrhosis of the liver as a disease entity or they have believed that differentiation of separate types was not feasible on the basis of anatomic differences. Others, notably Mallory,[105] Karsner,[82] and Rössle[158] believed such differentiation was possible. In recent years distinguishing features of certain types have become clear, and with time further delineation will become possible. Thus it now seems proper to differentiate from portal cirrhosis certain types on the basis of known etiology, and anatomic and clinical characteristics. These include *postnecrotic cirrhosis, cirrhosis of hemochromatosis, of hepatolenticular degeneration,* and *primary biliary cirrhosis.*

The term *portal cirrhosis* still is a repository, a name applied to several diseases which result in diffuse inflammation and fibrosis of the liver. Since the liver, like any other organ, has a limited number of ways in which it reacts to injury, there is little wonder that the final pathology from a variety of insults may appear to be similar. It has been shown by Himsworth[73] and others that repeated, sublethal injury with a poison such as carbontetrachloride may produce a finely diffuse cirrhosis of the portal type, whereas the same agent in greater dosage may produce the anatomic lesions of postnecrotic cirrhosis. Therefore, it is evident that anatomic classifications provide limited information. Ideal grouping should be made according to etiology. Here, too, this is not possible at present, since causative agents are not entirely established. Because of these limitations a mixed type of classification is retained, employing terms that are more or less conventional at the present time.

This and the following chapter deal with two of the commoner types of cirrhosis. The first is diffuse portal cirrhosis commonly associated with alcoholism and malnutrition and is referred to as *Laennec's cirrhosis.* The second type, *postnecrotic cirrhosis,* is a coarsely nodular variety, seen as a sequel to infectious hepatitis. The clinical and pathologic differentiation of these two types is by no means clear-cut. Occasionally, the lesions are mixed in type and defy classification. In certain instances the liver of a patient presumed to have died of posthepatitic cirrhosis shows morphologic changes of Laennec's cirrhosis, and in other instances postnecrotic cirrhosis is discovered in a patient whose

TABLE 25. CLASSIFICATION

PORTAL CIRRHOSIS	
1. Laennec's cirrhosis	*Synonyms:* Portal, alcoholic, fatty, atrophic, hypertrophic, nutritional
2. Kwashiorkor	*Synonym:* Malignant malnutrition
3. Miscellaneous	
A. Portal cirrhosis due to chemicals (carbon tetrachloride, phosphorus)	
B. Portal cirrhosis—etiology unknown	
POSTNECROTIC CIRRHOSIS	*Synonyms:* Toxic, posthepatitic, healed yellow atrophy, multiple nodular hyperplasia
1. Typical (coarsely nodular)	
2. Atypical (portal type—diffuse)	

clinical course suggested alcoholic (Laennec) cirrhosis. It is not possible to prove whether these exceptions are real or apparent. Because of our limited knowledge it seems more helpful to emphasize distinguishing features rather than to emphasize the confusion. In the ensuing chapters the more characteristic features of the two types will be stressed. The following classification, although not entirely satisfactory, will serve as a framework for the material to be presented (Table 25).

INCIDENCE OF LAENNEC'S CIRRHOSIS

Laennec's cirrhosis is world-wide in distribution, affecting all races and nationalities. In the Orient it is encountered particularly in China, India, Java and the Malay States. In South Africa, East Africa and in the Caribbean Islands a "nutritional" type of cirrhosis, similar in many respects to Laennec's cirrhosis, is widespread and constitutes one of the challenging public health problems of these areas. This disease, kwashiorkor, will be discussed separately. In Western Europe, North and South America cirrhosis is associated commonly with chronic alcoholism.

Descriptions of the disease vary somewhat from area to area. It appears likely that the differences are related to complicating conditions, such as malnutrition and intercurrent infections. Nutritional deficiency generally involves multiple factors which differ in separate regions of the world according to the staple foods available. The patients suffer from various deficiency diseases in addition to cirrhosis. In South Africa, for example, the livers contain a high degree of iron pigment not encountered elsewhere. In other areas amebiasis, malaria and parasitic infestations are commonplace. In these countries the patients suffer from multiple diseases; indeed, in many instances the hepatic lesions appear to be mixed or unclassifiable. It may be questioned, therefore, whether the term Laennec's cirrhosis should embrace these variants from classical descriptions of the disease. However, on the basis of clinical descriptions and pathologic findings it appears that by far the most prevalent cirrhosis corresponds to Laennec's cirrhosis.

Since cirrhosis of the liver is not a r
portable disease, the clinical incidence cann
be determined. The lack of standard nome
clature also renders figures from mortali
data unreliable, as pointed out by Karsner
In surveys of autopsy statistics by Row
tree,[159] de Jong,[33] Ratnoff and Patek[148] the
was considerable variability within the sar
country.

De Jong, in a compilation of 585,963 a
topsies from various parts of the world, fou
the incidence of cirrhosis to be less than
per cent in 254,525; between 2 and 3 p
cent in 209,037; greater than 3 per cent
122,401. Despite the limitations of such da
it is clear that the relative incidence is hi
in certain areas. In China,[208] Ceylon,[185] a
India[179] figures vary from 4 to 7 per cent
more. In East Africa an incidence of 6.7 p
cent[188] and in Chile 8.5 per cent[2] have be
reported.

Rowntree[159] found that in Europe
death rate from cirrhosis was highest in It
and lowest in Norway. Other reports sugg
unusually high rates in Switzerland (3.6
12%) when compared with those from G
many, Holland, Sweden and the U.S.S.R
Rolleston and McNee[154] have indicated t
death rates from cirrhosis in England
Wales fluctuate in accordance with dea
due to alcoholism. This also has been e
phasized by Rowntree.[159]

In the United States mortality data on
rhosis show wide differences. For exam
in 4 series of autopsies incidences of 3
cent,[105] 6 per cent,[19] 2.2 per cent[124] and
per cent[47] have been given. The usual ra
has been from 2 to 4 per cent of autops
On the West Coast, presumably due to
Asiatic population, the incidence has b
somewhat higher than the average. In B
ton[150] and New York[148] cirrhosis seems
have a predilection for persons of Italian
Irish stock.

The widespread occurrence of Laenn
cirrhosis suggests that environmental fac
are related to its incidence more significa
than are racial factors.

ANTECEDENT FACTORS (ETIOLOC

DIET

Attention was first directed to the pos

role of dietary factors in countries where alcoholism is an unimportant feature in the background of the disease. In a report of 84 cases of cirrhosis of the liver in China, Yang[208] in 1928 stated that over 70 per cent were in the laboring group subsisting on coarse carbohydrate foods. In 1933 Rao[147] observed that the diets of patients with cirrhosis of the liver in Southern India were deficient in protein, fat and vitamins, especially A, C and D. In 1934 Yenikomshian[209] reported that patients in Syria with hepatic cirrhosis lived on a diet chiefly of bread and legumes, a diet poor in protein and vitamin A. In 1937 Tyagaraja[185] noted that the diets of patients with cirrhosis in Ceylon had been deficient in nitrogenous foods and vitamins. Although the above authors stressed the poor dietaries in the background of cirrhosis, other factors, such as enteric fevers, malaria and parasitic infestations were considered by them to be of primary etiologic importance. No systematic attempt to influence the course of the disease by dietary means was reported.

In the Western hemisphere more than 50 per cent of patients with Laennec's cirrhosis are chronic alcoholics. The frequent association of chronic alcoholism with deficiency diseases, such as pellagra and beriberi, has been well established by studies of Spies,[172] Strauss[174] and his co-workers, Romano[155] and others. Likewise, in patients with "alcoholic" cirrhosis it has been observed that their dietaries have been deficient in protein and dairy foods, and that they frequently showed signs of coexisting deficiency diseases.[79, 168, 129, 200] When such patients were fed a highly nutritious diet, the clinical improvement that followed seemed to be beyond chance expectation.

More recently extensive surveys of "nutritional" cirrhosis in South Africa,[32, 59] East Africa[180] and Jamaica[195] have indicated that cirrhosis of the liver is widespread in these areas. Although the type of cirrhosis does not conform strictly to Laennec's cirrhosis, there are basic similarities. Moreover, the favorable response to dietary treatment in the form of skimmed milk supplements has been dramatic.

On the basis of clinical observations it has been postulated that dietary deficiency may play an etiologic role in Laennec's cirrhosis. This concept has been strengthened greatly and has achieved scientific stature by virtue of a series of brilliant experimental studies. Since this aspect of cirrhosis is discussed elsewhere in detail it will be mentioned only in passing. Basic to this work were the studies by Best and his associates[12, 13] and Tucker and Eckstein[40, 182] who elucidated the nature of the fatty liver and its relation to the metabolism of choline and methionine, and the experiments of DuVigneaud[38] and his associates who demonstrated the biologic interrelationship of choline and methionine. In subsequent studies by Chaikoff,[26] Webster,[201] György,[63] Daft,[31] Blumberg[17] and their respective co-workers cirrhosis of the liver was produced experimentally by means of diets low in casein (and in methionine). The lesions were prevented by the addition of the lipotropic substances to the low-casein diets, thus indicating a specific role of choline or methionine in the production and the prevention of the disease.

Although experimental nutritional cirrhosis and human Laennec's cirrhosis may not be the same disease, the analogy is very close. At the present time, therefore, the evidence suggests that dietary deficiency is a primary etiologic factor in Laennec's cirrhosis.

ROLE OF ALCOHOL

The association of alcoholism and cirrhosis has long been known. Vesalius[167] and Fernel[167] are said to have recognized this relationship. Hart (1633), Bailie (1812) and Bright (1827) observed that the disease was seen commonly in those who imbibed spiritous liquors. In general, the incidence of alcoholism in cirrhosis has been higher in clinical series of cases than in those based upon postmortem findings. This might be anticipated, since the history of alcoholism usually is not elicited when it is not suspected. In several clinical series reported from Europe and the United States the incidence of alcoholism in cirrhosis has varied from 52 to 86 per cent, with a mean of about 75 per cent; in other series based upon postmortem findings the figures ranged from 20 to 75 per cent with a mean incidence of about 50 per cent.[148] The type of alcoholic beverage apparently bears no relation to the severity or the frequency of the disease.

Parallel changes in the incidences of alcoholism and cirrhosis reveal further their close relationship. When the consumption of liquor was curtailed, as during Prohibition in the United States and during World War I, there was a corresponding decline in deaths from cirrhosis. Upon repeal of Prohibition there was a sharp rise in the death rate from cirrhosis, reaching a peak of 8.5 per 100,000 population in 1937.

The duration of alcoholism preceding the onset of hepatic failure has averaged about 15 years in our experience. The steady drinker is more likely to acquire the disease than the "spree" drinker, presumably because the steady drinker suffers from chronic malnutrition.

Although alcoholism is a frequent precursor to cirrhosis, the incidence of cirrhosis among alcoholics is relatively low. It has been estimated variously that from 1 to 30 per cent of chronic alcoholics develop cirrhosis.[148] Since alcoholism generally is not reported unless the patient is institutionalized, accurate data are not obtainable. Nonetheless, the incidence is not impressive, and one might infer that alcoholism alone does not produce cirrhosis. The fact that the disease is seen commonly in countries where alcoholism is rare, notably India, also supports this interpretation.

In a review of experimental cirrhosis of the liver in laboratory animals Moon[114] cited many unsuccessful attempts to produce the disease by the administration of alcohol. In more recent years the problem has been investigated further. Lowry and his co-workers[102] reported that in the production of nutritional cirrhosis in the rat (on a low-casein diet) the substitution of 20 per cent alcohol for water intensified the disease. Best and his co-workers,[11] however, indicated that this effect may be due simply to the substitution of added calories, since with isocaloric diets the addition of sucrose had the same effect as alcohol in comparable experiments.

Other recent clinical studies have suggested that ingestion of alcohol renders the liver vulnerable to certain toxins, such as carbon tetrachloride. There is also evidence to suggest that alcohol may interfere with intermediary metabolism of carbohydrate and possibly of choline.

Nevertheless, it has been possible to feed alcohol to patients with Laennec's cirrhosi without incurring apparent harm. In one experiment[129] 4 patients recovering from hepatic failure were fed 9 ounces of 40 per cen alcohol daily for 6, 6, 14 and 18 months respectively. This was taken in addition to nutritious diet supplemented with vitamin complex. The patients continued to mak progressive recovery from their disease Volwiler reported a similar experience wit one patient.

Although a hepatotoxic effect from alcoho cannot be excluded, the evidence at presen indicates that its role is of secondary importance in the etiology of cirrhosis. It seem probable that the correlation between alc holism and cirrhosis of the liver is due largel to coexisting nutritional deficiency.

Relation to Infectious Hepatitis

Whether or not acute infectious hepatit leads to Laennec's cirrhosis is an unresolve problem. In several large series of cases[19, 2 47, 54, 86, 194] infectious hepatitis was not liste among etiologic factors of Laennec's (c portal) cirrhosis. Presumably, it was not co sidered, or it was inconspicuous in the background. In other series,[16, 45, 48, 130, 147, 148, 1 where the possibility was investigated, th incidence of antecedent hepatitis has show considerable range, with values from 1.4 13 per cent. Two recent series[2, 75] are especial interest because of the relative high incidence of antecedent hepatitis an because they included control groups patients. In a study of 100 cases Laennec's cirrhosis Howard and Watson encountered 17 with a story of previo hepatitis, in contrast with a control hospit group of only 3. This is a significant diffe ence. Armas-Cruz[2] and his associates r ported an incidence of 25.7 per cent in series of 208 cases, as compared with 18 per cent of corresponding controls. In th series the differences between the two grou was not considered to be significant. T basis for these variations is not evident unle it is related to regional factors. Howard a Watson pointed out that the ratio of femal to males was greater, and the incidence of alcoholism lower in their cases than in other reported series, suggesting a somewhat different type of case material.

Analysis of the sequelae of infectious hepatitis also provides diverse results and interpretations. In several large series concerned with chronic or relapsing infectious hepatitis no mention has been made of the development of Laennec's cirrhosis. For example, no instances were cited in 431 cases reported by Barker, Capps and Allen[6]; nor in 350 cases reported by Kunkel and his associates[93]; nor in 217 cases reported by Klatskin and Rappaport.[87] Likewise, in a selected group of 112 cases Post and his associates[141] described 4 instances of postnecrotic cirrhosis but none of the Laennec type. In a series of 140 cases of hepatitis Fernando and Thanabalasunderam[53] cited several instances of massive necrosis and of postnecrotic cirrhosis (toxic cirrhosis) but none of the Laennec type.

However, there are several reports of cases studied postmortem[4, 15, 34, 80, 198] and numerous reports[3, 35, 90, 91, 156, 169] of cases studied by means of serial biopsies in which the development of portal or Laennec's cirrhosis has been cited. Although the accurate definition of cirrhosis from needle biopsy is often impossible, there is no basis for questioning postmortem findings unless the classification of cirrhosis varies with different observers.

This actually appears to be the present difficulty, for what one observer might designate Laennec's, another would designate postnecrotic cirrhosis, as amply shown at a conference of 8 pathologists familiar with this field.[104] A recent article by Baggenstoss and Stauffer[4] throws further light on this subject. They compared 43 autopsied cases of "alcoholic" cirrhosis with 43 cases of "posthepatitic" cirrhosis. The latter comprised patients whose histories strongly suggested infectious hepatitis as the causative agent. Although most of the latter conformed to the description of postnecrotic cirrhosis, there were 7 instances in which the morphology resembled the finely diffuse changes of Laennec's cirrhosis. It seems reasonable that this should be so. Experimentally,[25, 114] all gradations from massive necrosis and atrophy to a finely diffuse cirrhosis can be produced by hepatotoxins, depending upon the dosage, the agent employed and the chronicity of the injury. If a chronic infectious hepatitis exists, it should produce on occasion a finely diffuse cirrhosis.

Therefore, it appears that a diffuse, portal type of cirrhosis may follow an episode of infectious hepatitis. The morphologic features of this cirrhosis at autopsy may be indistinguishable from Laennec's cirrhosis. For reasons previously stated (cf. introduction) the writer prefers to consider this as a variant of postnecrotic cirrhosis rather than true Laennec's cirrhosis.

SYPHILIS AS A PREDISPOSING FACTOR

The incidence of syphilis in patients with cirrhosis of the liver appears to be relatively high. In several series it has been reported to occur in from 8 to 28 per cent of the cases, the figures being based upon serologic or clinical data, or both. The mean value in 10 series[19, 47, 48, 54, 130, 148, 165, 166, 194, 209] comprising 1,429 cases was 14.6 per cent. Because of this frequency it has been suggested that either the spirochete or antisyphilitic therapy may be etiologic factors. The evidence at present indicates that the only characteristic hepatic lesion of syphilis[65] is that of hepar lobatum, in which deep lobulations result from gummata (cf. Syphilis of the Liver). There is no doubt that arsphenamine and its derivatives are hepatotoxic, but the incidence of cirrhosis would appear to bear little relation to the extent of arsphenamine therapy. However, one encounters occasional instances in which nonalcoholic patients develop a diffuse, portal type of cirrhosis after prolonged, intensive arsphenamine therapy, and the possibility remains that on rare occasions this may result from drug intoxication. More impressive is the finding that hepatitis resembling acute homologous serum hepatitis may be encountered in patients receiving antiluetic therapy, and it is Dible's[35] contention that these indeed represent homologous serum ("syringe") hepatitis. It is conceivable that a certain per cent of these develop chronic hepatitis and diffuse cirrhosis which could be similar morphologically to Laennec's. However, the majority of such cases probably would fall into the group of postnecrotic cirrhosis, such as described by Baldridge.[5]

The concurrence of syphilis and Laennec's cirrhosis raises two further questions, namely, the incidence of cirrhosis in persons with syphilis, and the incidence of syphilis in chronic alcoholics without cirrhosis. Information on the first is not at hand. However, it has been shown that the incidence of syphilis in alcoholics is high,[125] and that the association of alcoholism and syphilis in Laennec's cirrhosis is no more frequent than might be expected by chance.[48, 148] They exert no synergistic effect.

It seems fair to conclude that syphilis occurs more frequently in these patients than in the general population, but that it probably is not an important predisposing factor in the over-all incidence of Laennec's cirrhosis.

Other Antecedent Factors

Chemicals such as *carbon tetrachloride, phosphorus* and *chlorinated naphthalenes* are common causes of toxic hepatitis in industry. In certain instances this appears to have progressed to portal cirrhosis. Workers whose diets have been poor, and especially those who drink alcohol to excess, are prone to poisoning by these agents. However, these "chemical" cirrhoses doubtless comprise a very small per cent of the total number of portal cirrhoses.

The incidence of Laennec's cirrhosis is increased in the presence of certain diseases, such as *diabetes mellitus, thyrotoxicosis, malaria* and *bacillary dysentery*. The relation of these diseases to Laennec's cirrhosis appears to be indirect. It should be pointed out that these same diseases often are complicated by malnutrition, which in turn would enhance hepatic injury.

PATHOGENESIS

The pathogenesis of Laennec's cirrhosis is an unsolved problem. It is not established whether the primary lesion involves injury to the liver cell, infiltration with fat, or overgrowth with connective tissue. Most observ
ers believe that the primary lesion involve
cellular damage, that fatty changes are o
secondary importance since other types o
cirrhosis occur without an intermediate fatt
stage. The stimulus to fibroblastic ove
growth is unknown.

PATHOLOGY

The liver is diffusely nodular or granula
leathery in texture and of reddish-yello
color, occasionally mottled with green. Th
size of the organ is variable, with weigh
ranging from 900 to 3,000 Gm. As a rul
the liver is moderately reduced in volum
and weight.[82, 86, 148, 153] Increased size of th
liver usually is due to the presence of fat.[30,
From clinical observations there appears
be a tendency toward shrinking with pr
gressive hepatic failure. The discoloratio
depends upon the degree of jaundice, fa
fibrosis and congestion present.

The size of the nodules varies from le
than 1 mm. to more than 1 cm. in diamet
(Fig. 124 A, B). At times larger nodul
and broad scars are seen which resemble th
gross appearance of postnecrotic cirrh
sis.[4, 82] Indeed, in certain instances classific
tion is impossible. Such instances Mallory
was inclined to designate as "unclassifie
cirrhosis. In general, however, the nodul
are diffuse and fine, as revealed especia
on the cut surface.

The chief microscopic feature is wid
spread overgrowth of connective tissue whi
destroys the normal lobular structure (F
125). Early fibroblastic changes are mo
conspicuous in the peripheral zones in t
region of the portal triads.[82] From the por
areas bands of connective tissue exte
toward other portal areas. They may inva
the cords of liver cells as well. This is som
what at variance with the findings in expe
mental nutritional cirrhosis in the rat,[67]
which early changes are seen in the region
the central veins from which the connecti
tissue projects toward the portal areas. T
differences may be more apparent than re
since the developmental stages in hum
disease are more difficult to establish. T
cellular infiltration in the portal triads

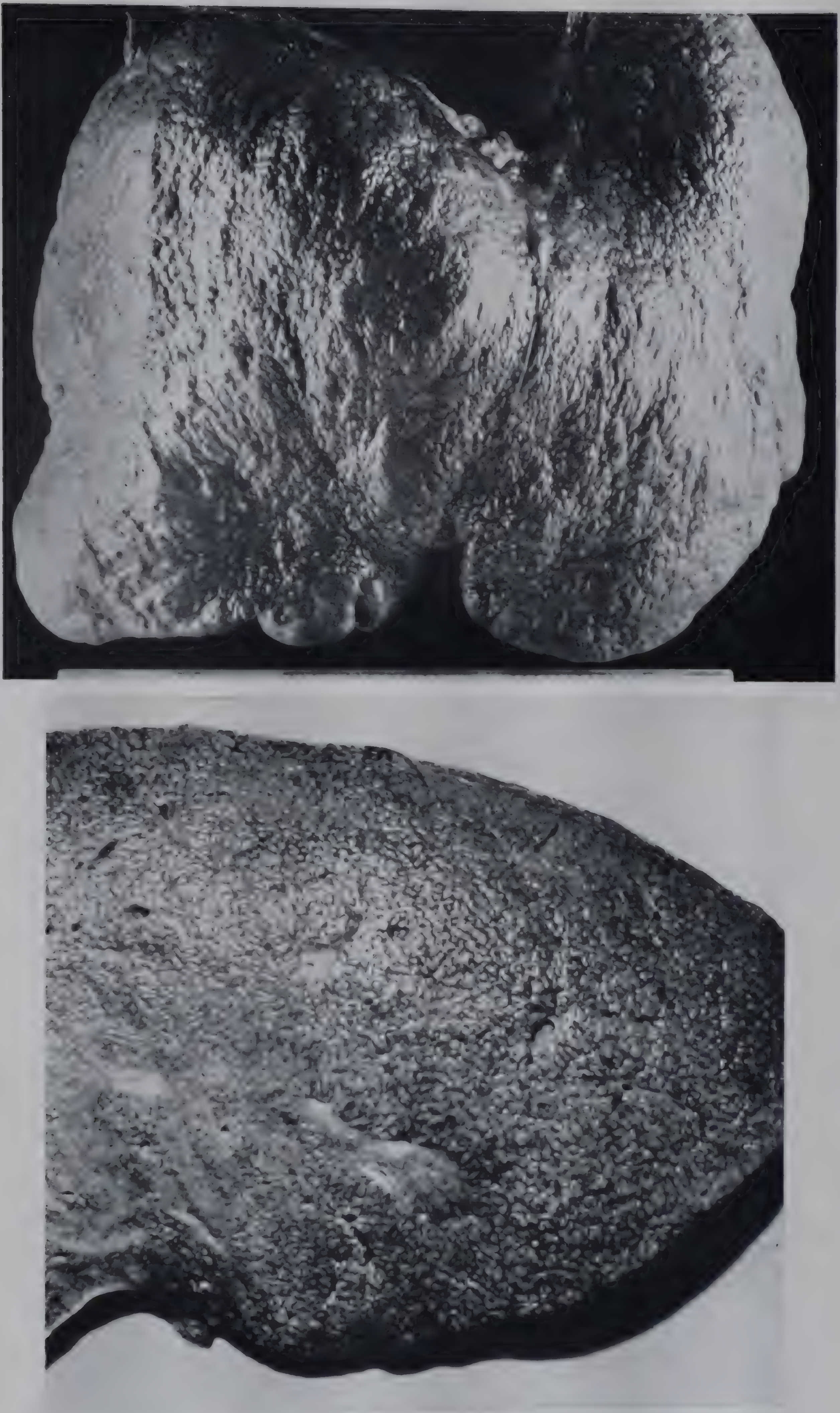

Fig. 124. Laennec's cirrhosis. (A, *top*) The liver is large, pale and uniformly finely nodular. (B, *bottom*) Sectioned surface of the cirrhotic liver demonstrating the comparatively fine nodularity and regularly disposed delicate fibrous tissue.

predominantly lymphocytic or histiocytic, although polymorphonuclear cells may be present as well. Some observers have described preponderance of the latter cells.[4] Possibly the differences may relate to the stage of the cirrhotic process, since death frequently is due to causes other than hepatic failure. In the region of the triads proliferating bile ducts also may be seen.

Parenchymal liver cells show degenerative changes, in particular fatty vacuolization, hyalin deposits and scattered small foci of necrosis. In other areas there are signs of cellular regeneration. Fatty vacuolization may be extreme in early stages of the disease, whereas in later stages the fat is inconspicuous. The sequences in the development and the disappearance of fatty vacuolization have been traced vividly by Hartroft and his associates in studies of experimental nutritional cirrhosis (cf. Chap. 4). In the past, fatty cirrhosis has been considered as a disease entity. Current ideas favor the concept that fatty vacuolization represents either an early stage in the disease or that it is an associated phenomenon but not necessarily an integral part of the disease process. Serial biopsies of the liver have shown that fatty changes may regress within a few weeks in patients fed a nutritious, protein-rich diet.[140, 190] Mallory[10 described hyalin droplets in the liver cells peculiar degenerative changes that are common to "alcoholic" cirrhosis. These droplet may coalesce into larger masses within th cells. Although such changes are encountere far more frequently in Laennec's cirrhosi than in other types they are not pathognomonic of the disease.[4, 113] In scattered area the cells appear to have lost their nuclei. I others, large cells with deeply stained nucle —at times multinucleated—are seen. The may be several times the normal size. Suc cells are considered as regenerating cells.

A striking feature is the displacement o vascular channels. Small branches of th portal vein are seen in the connective tissu septa, where they appear to be compresse by the regenerating nodules.[84] The hepati veins may be unidentifiable or may be displaced eccentrically in the lobule. The extreme degree of change in vascular patter has been demonstrated by means of injectio studies by McIndoe[109] and others.[192] Th finer arborizations of the portal tree are los and only the stenosed main trunks remai Whereas the portal venous system transpor the major portion of inflow blood of th normal liver (approximately 80% und

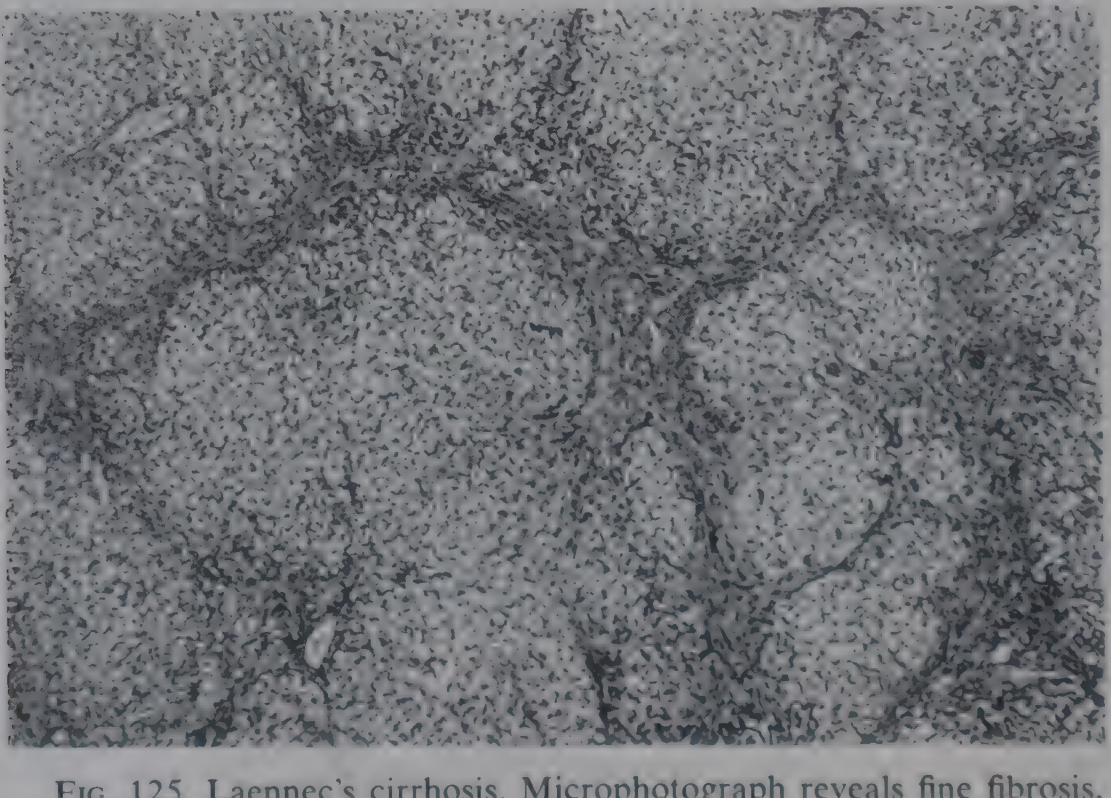

FIG. 125. Laennec's cirrhosis. Microphotograph reveals fine fibrosis, micronodulation and pseudolobule formation. Intracellular fat vacuolization is prominent.

standard conditions), there is good evidence that the hepatic artery assumes a larger burden in the presence of cirrhosis. Anastomoses between the two inflow systems have been demonstrated in the presence of cirrhosis.[107] It is possible that this admixture increases further the elevated portal venous pressure produced by bands of connective tissue. Engorged tributary veins draining the mesentery, the spleen and the stomach are commonly seen, as well as many collateral veins over the abdominal wall and along the inner surface of the peritoneum. The most serious consequence of increased portal venous pressure is the rupture of veins in the lower esophagus and the cardiac end of the stomach, accounting for about 20 to 30 per cent of fatal cases.[4, 148]

Splenomegaly occurs in from 70 to 85 per cent of the cases. The true size and weight of the spleen is doubtless greater than the recorded weight in many instances because of shrinkage from loss of blood at the time of autopsy. Histologic changes vary from simple hyperemia to extensive fibrosis. In the later stages the pulp spaces contain little blood, the trabeculae become increased in size, the malpighian bodies become smaller, and fibrosis may appear around the central vessels. The term "congestive splenomegaly" implies that the enlargement is due to congestion or stasis, but it seems more likely that it is related to the duration and the intensity of portal vein hypertension. McMichael and others have pointed out the frequent occurrence of sclerosis of the portal vein and its branches and have suggested that this was related to increased venous pressure. The studies of Thompson,[177] Rousselot and Whipple clearly established the association of splenomegaly with increased portal venous pressure. No essential differences were detected between the splenomegaly of cirrhosis and the splenomegaly of extrahepatic block in the portal venous system. On this account they concluded that splenomegaly was mechanical in origin.

Others[24, 111, 149] have suggested that toxic or infectious agents may play a contributory role in splenomegaly of cirrhosis. Although this possibility cannot be excluded, the present evidence suggests that increased pressure in the portal vein is primarily responsible. The subject has been reviewed critically by Moschcowitz.[119]

Secondary changes, such as jaundice, ascites and peripheral edema, are generally present in fatal cases.

Signs of malnutrition and specific deficiency states are frequent.[130] These include pellagrous changes in the skin, atrophy of the tongue papillae, polyneuritis and degenerative changes in the brain stem.

Signs of hormonal derangement are found, especially in the male.[99] These include atrophy of the testes, gynecomastia, and decrease in body hair.

Chronic pancreatitis is seen in about 15 per cent of the cases. This lesion also is seen in chronic alcoholism without cirrhosis, and its relation to cirrhosis may be incidental.

Peptic ulcer is seen in from 5 to 15 per cent of the cases and at times may cause severe hemorrhage. It is not clear whether this complication is more frequent than the expected incidence of peptic ulcer of a control population.[164]

Infections have been contributory causes of death in about 25 per cent of the cases. The most commonly encountered are bronchopneumonia, peritonitis, phlebitis, phlegmonous enteritis, glomerulonephritis and endocarditis. Although tuberculous peritonitis and miliary tuberculosis were formerly rather frequent complications, these have been encountered rarely in recent years.

LATENT CIRRHOSIS

Cirrhosis of the liver may be asymptomatic. Of 167 cases examined postmortem, Rolleston and McNee[154] found 87 that had been latent during life. Similarly, McCartney[108] reported that 35 per cent of 245 autopsied cases of portal cirrhosis had been latent during life. In reviewing the charts of 865 patients with the diagnosis of cirrhosis of the liver Ratnoff and Patek[148] found 386 with adequate clinical signs of the disease and 49 in which the diagnosis was discovered postmortem or at operation. The remaining 430 cases were excluded because of insufficient data.

The average age at death is approximately the same for latent and active cases. The disease is no more advanced in older than in younger patients with latent cirrhosis. From this it has been inferred[108] that the disease can be arrested. Clinical and experimental observations in recent years also support this interpretation.

Patients who recover from hepatic failure and lead an exemplary life (i.e., abstain from alcohol and follow a nutritious diet) appear to have a normal life expectancy, even though their livers show considerable damage. However, they seem to be more delicate, more vulnerable to intercurrent illnesses than the average healthy adult. Experience with this group is too limited to permit more than a clinical impression.

CLINICAL FINDINGS

SYMPTOMS

The onset of Laennec's cirrhosis is usually gradual. The early symptoms may be so vague that one cannot ascertain the time of onset. The patient often states that he has had indigestion for years, that he lacked stamina or felt old before his time but was unaware of actual illness until abdominal swelling, jaundice or hemorrhage supervened.

The initial symptoms and signs of liver failure, as determined from a large group of patients,[148] are listed in Table 26.

TABLE 26. INITIAL SYMPTOMS AND SIGNS IN 386 CASES OF LAENNEC'S CIRRHOSIS[148]

SYMPTOMS	NUMBER OF CASES	PER CENT OF CASES
Swollen abdomen	107	27.7
Abdominal pain	48	12.4
Hematemesis	39	10.1
Edema of legs	36	9.6
Jaundice	34	8.8
Nausea and vomiting	29	7.5
Weakness	22	5.7
Abdominal distress	17	4.4
Bleeding, epistaxis	15	3.8
Diarrhea	14	3.6
Anorexia	9	2.3

In 46 cases, multiple symptoms were listed at onset.

With the frank development of the disease, symptoms are more pronounced. Table 27 includes data from several series of cases. Although differences exist, possibly relate
to regional factors, the salient features a
present with similar frequency in the sever
series listed.

Anorexia is an early and telltale sympton
often not understood by the patient so muc
as by his family. Meals are scanty and ha
hazard. This history, to be sure, is comm
to alcoholics without cirrhosis, but the pe
sistent, chronic malnutrition of the stea
drinker is particularly typical of the cirrhot

Weight loss occurs in about one half
the patients. Others show surprisingly litt
change, and it seems evident that alcoh
must provide a large share of their calo
intake. Indeed, beer drinkers with cirrho
are often obese, and their obesity tends
obscure an underlying state of malnutriti

Nausea, vomiting, gagging, flatulence a
frequent symptoms. Saundby[148] and Aska
azy[148] have attributed these, at least in pa
to associated alcoholic gastritis.

Gaseous distention of the abdomen m
distress patients for months or years p
ceding the onset of ascites.

Abdominal pain is present in varying
gree. It has no peculiar attributes in cirrho
It may be mild, dull, sharp, wavelike,
steady. It is more apt to occur shortly af
meals. It may be confined to the region
the liver or referred to the epigastrium or
lower abdomen. Fairly often it is associa
with tenderness of the liver and occasiona
with friction rubs over the liver or the sple
This symptom has been attributed to capsu
swelling, perihepatitis, spasm of the bili
ducts, or to intermittent vascular spasm. I
likely that no single mechanism can acco
for its variegated pattern. In general,
dominal pain is experienced during act
liver failure and abates with improvem
Severe, boring, constant pain radiating to
posterior thorax should suggest the possi
ity of penetrating peptic ulcer or of su
imposed carcinoma of the liver.[204]

Hematemesis. This dreaded symptom
been estimated to occur in from 8 to 30
cent of patients with cirrhosis and is one
the chief causes of death. Wang reported
incidence of 9 per cent; Eppinger repo
an incidence of 8 per cent; in the experi
of others[2, 48, 130] hematemesis has occu
in from 24 to 34 per cent of the cases. H

TABLE 27. SYMPTOMS IN LAENNEC'S CIRRHOSIS
(Per Cent Incidence)

	PATEK ET AL.[130]	RATNOFF AND PATEK[148]	FLEMING AND SNELL[54]	FAGIN AND THOMPSON[48]	ARMAS-CRUZ ET AL.[2]
No. of cases	124	386	200	71	208
Average age	48.8 yr.	50 yr.	50.4 yr.	48.4 yr.	45 yr.
Males	65%	69%	75%	100%*	70%
Alcoholism	77	54	42.5	79	78
Weight loss	89	53	58	34	49
Anorexia	78	35	. .	. .	86
Nausea and vomiting	51	30	30	44	72
Abdominal pain	50	31	46	48	60
Epistaxes	40	18	. .	10	19
Hematemeses	34	27	13	21	31
Purpura	. .	9	. .	. .	. .
Weakness	. .	21	. .	38	94
Diarrhea	. .	20	18	11	30
Abdominal distress	. .	16	. .	. .	75
Nocturia	. .	26		. .	.

* Marine Hospital.

orrhage usually arises from rupture of one or more esophageal varices and occasionally from veins in the cardiac portion of the stomach. In roentgenographic studies the veins are seen to be greatly enlarged and tortuous, whereas at autopsy they are collapsed and at times so inconspicuous that the site of bleeding cannot be detected. Occasionally, peptic ulcer is the basis for hematemesis. This possibility should be considered, since from 5 to 15 per cent of patients with cirrhosis have demonstrable peptic ulcer. Also, it may be emphasized that massive blood loss from esophageal or gastric varices can occur without hematemesis, as well as slow leakage into the gastro-intestinal tract. Frequently, the patient has a foreboding of the event. He feels weak and anxious and complains of epigastric fullness and nausea. These symptoms may precede vomiting by several hours. However, hematemesis also occurs quite without warning. With massive

TABLE 28. SIGNS IN LAENNEC'S CIRRHOSIS
(Per Cent Incidence)

	PATEK ET AL.[130]	RATNOFF AND PATEK[148]	FLEMING AND SNELL[54]	FAGIN AND THOMPSON[48]	ARMAS-CRUZ ET AL.[2]
No. of cases	124	386	200	71	208
Ascites	93%	78%	100%*	63%	74%
Palpable liver	79	75	55	70	71
Peripheral edema	60	61	58	59	41
Jaundice	67	65	45	52	70
Vascular spiders	62	15	. .	. .	45
Collateral veins	61	24	34	41	63
Palpable spleen	55	44	32	24	31
Fever	49	24	. .	49	30
Esophageal varices	48	. .	. .	. .	. .
Glossitis	48	. .	. .	. .	. .
Mental change	38	. .	. .	. .	16
Polyneuritis	36	13	. .	. .	. .
Herniae	33	9	. .	17	8
Clubbed fingers	18	5	. .	. .	
Hydrothorax	17	6	. .	10	9

* Selected with ascites.

bleeding, fever and azotemia are usually seen. It is believed that fever is due to the retention of blood in the intestinal tract. Azotemia is ascribed partly to the retention of blood and also to impaired renal excretion due to shock.[78, 163]

PHYSICAL SIGNS

The chief signs of Laennec's cirrhosis are listed in Table 28. These data, derived from several series of cases, apply for the most part to hospitalized patients in failure and reflect an advanced stage of the disease. There is fair agreement in these studies with respect to classical features: ascites, jaundice, edema, hepatomegaly, splenomegaly. Less conspicuous signs show wider differences which probably relate to the special interests of the observers. The series cited are only a few of the many reported clinical studies. In addition to those listed, data have been derived from reports by Henrikson[69]; Wang[194]; Chapman, Snell, and Rowntree[27]; Eppinger[45]; and several texts, such as Rolleston and McNee,[154] Lichtman,[97] Tumen and Bockus.[184]

Studies limited to autopsied cases are not included in the table, since they deal only with fatal cases.

Fever is commonplace. It is typically intermittent, with afternoon rises to 100° or 101° F. and accompanied by normal or slightly increased white blood cell count. Higher temperatures and pronounced leukocytosis are caused more often by intercurrent infections. However, occasional instances of uncomplicated Laennec's cirrhosis do occur with fever and leukocytosis as conspicuous features. This type of response is seen in florid, active stages of the disease, so-called fatty liver or fatty cirrhosis, which may run a fulminant course.[83] Jaundice is apt to be conspicuous in this group.

Subsidence of fever is one of the early, favorable signs in recovery from the disease.

Ascites is probably the most characteristic sign of the disease. Erasistratus[148] was said to have associated ascites with hepatic disease. Morgagni[148] described a patient with ascites, which he attributed in part to impeded blood flow through the vena portae and to the scirrhous state of the liver. In several large series of autopsied cases[33, 89, 154, 191] the incidence of ascites varied from 57 t 85 per cent. It is curious that the incidence i these fatal cases is no greater than that foun in clinical series with less-advanced diseas The reason for this is not clear.

Ascitic fluid has the characteristics of transudate.[100] Rarely, the fluid may b chylous. The protein content bears a dire relationship to the concentration of plasm proteins, since there is an appreciable tran fer of protein across the portal vascular ba rier.[128, 178] Generally, the concentration is i the range of 0.5 to 1.5 Gm. per 100 cc.

The mechanism for the formation ascites is not fully clarified. Both system factors and local factors operating at th portal vascular bed appear to be involve In the presence of hepatic disease, wheth cirrhosis of the liver or acute hepatiti there is a tendency toward the retentic of water and salt[1, 52, 94, 106] and an increase plasma volume.[133] This avidity for sodiu and water has been attributed to the actic of antidiuretic substances. Ralli[146] and h associates have indicated that the antidiuret hormone may be pituitary in origin, where Van Dyke[186] and Leiter[203] and their assoc ates present evidence that throws doubt upc this hypothesis. Others[42, 44] have pointed o that the adrenal cortex may be involved, that increased circulating estrogens m favor the retention of fluid in hepatic diseas It seems plausible that hormonal factors a implicated, but their nature is not establishe Whether they act by binding salt and wat in the tissues or by means of a renal barri or both, is not known. Certain studies[96] ha indicated a decrease in glomerular filtrati rate in patients with cirrhosis and ascit whereas others[46, 128] have found no consta changes in glomerular or tubular function

In order to explain the localization of flu within the peritoneal cavity it has been a sumed that forces acting at the portal vasc lar bed likewise must be operative. Clinic studies have attributed ascites formation increased portal venous (capillary) pressu and lowered serum osmotic pressu due to hypoalbuminemia. Experimen studies[110, 189] with dogs tend to confirm t concept, since ascites can be produced ligation of the inferior vena cava above t liver or by ligation of the portal ve together with plasmapheresis. Several reports[122, 142, 184] have shown that ascites occurs chiefly in those patients whose serum albumin is decreased or whose osmotic pressure is correspondingly low.[14, 23, 71] Ascites tends to form when the serum albumin falls below a value of 3.1 Gm. per cent[142] or a serum osmotic pressure below 260 mm. H_2O. Although this correlation has been good in the large majority of cases, there are numerous exceptions to it. Ascites has formed in the presence of serum osmotic pressure above this "critical" level and has failed to occur in the presence of osmotic pressures below this level.[128, 146]

More elaborate studies[57, 76, 106, 110] of osmotic pressure relationships at the portal vascular bed have been carried out in recent years but have failed to clarify fully the local conditions governing ascites formation. It has been shown that there is a free interchange of water, protein and electrolytes between the blood plasma and the ascitic fluid; that a state of dynamic equilibrium is maintained between the osmotic pressure of the plasma and that of the ascitic fluid in accordance with Starling's concept.[173] In patients with Laennec's cirrhosis the difference or gradient between the plasma osmotic pressure and the ascitic osmotic pressure is consistently higher[57, 106] than in cases in which ascites is not related to hepatic disease (nephrosis, ovarian tumor). Doubtless, this large difference in osmotic pressure reflects the increase in effective portal capillary pressure in cirrhosis.

In summarizing this problem at the present time it appears that multiple factors are involved in the formation of ascites in cirrhosis of the liver: (1) There is a tendency to retain sodium and water. (2) This may be due to hormonal "antidiuretic" factors. (3) Whether the retention is exerted primarily in the extrarenal tissues or is secondary to a fault in renal excretion, or both, is not established. (4) The localization of fluid in the peritoneal cavity seems to be related to increased portal venous (capillary) pressure, to decreased plasma osmotic pressure and possibly to increased portal capillary permeability. It should be added that experimental studies in dogs[189] show that a block in the lymphatic channels draining the peritoneum can produce ascites. Whether or not this has its counterpart in human cirrhosis remains to be demonstrated.

Edema. The mean incidence of edema, as determined from 11 series of cases, was 61 per cent, with values ranging from 35[37] to 87 per cent.[147, 194] The highest values were reported from the Orient, and they may be due in part to coexisting beriberi. In others, congestive heart failure may be present, but this appears to be an unimportant factor in the large majority of cases.

Edema may appear as an early sign, and it may precede the formation of ascites.[27, 148] Fagin and Thompson[48] recorded edema as the earliest symptom in 13 of 71 patients. Wang[194] stated that about one third of his patients developed edema before ascites; one third, coincident with ascites; and one third, after the appearance of ascites. Almost always it is accompanied by hypoalbuminemia, which in turn has been considered a primary cause for edema. The rapid disappearance of peripheral edema (in contrast with ascites) after the intravenous administration of concentrated human albumin solution strengthens this concept.[178]

In many patients peripheral edema fluctuates with the amount of ascites present. After abdominal paracentesis, for example, edema may decrease sharply. It seems likely that both decreased colloid osmotic pressure from hypoalbuminemia and increased intra-abdominal pressure from ascites play a part in the formation of edema.

Hydrothorax occurs in a significant number of patients with Laennec's cirrhosis, and in almost every recorded instance it has been associated with ascites. In several series the incidence of hydrothorax has varied from 6 to 35 per cent, the more usual range being 10 to 15 per cent. The fluid generally has the characteristics of a transudate but frequently shows increased red blood cells microscopically.[62, 187] A few instances of grossly bloody pleural fluid have been reported.[29]

The mechanism has not been fully revealed. In several patients we have found that Evans blue dye or India ink injected into the peritoneal cavity was soon detected in the pleural fluid. The reverse flow was not encountered. Therefore, it seems likely that ascitic fluid traverses the diaphragm via the lymphatics or other vascular channels. This direction of flow has been demonstrated clearly in cases of Meigs's syndrome.[112] Occasional cases suggest that there may be open communications between peritoneal and pleural spaces.

Jaundice. Clinical jaundice appears in about one half of the patients at some time in the course of the disease. In 12 series of cases the mean incidence was 52 per cent, with a range of 34 to 67 per cent. Doubtless, the incidence of jaundice would be higher if subclinical icterus were included in the data. Jaundice, in patients with cirrhosis of the liver, indicates activity of the disease. Frequently, it is the presenting sign of hepatic failure. In 208 cases cited by Armas-Cruz et al.[2] jaundice was the initial symptom in 116 cases—a figure somewhat higher than in most studies. In the large majority of patients jaundice is moderate or mild. Frequently, it is detected only by laboratory test. Jaundice clears with other signs of improvement and tends to increase with other signs of failure. However, it is not an essential companion to hepatic failure. For exa
ple, in 217 fatal cases Evans and Gray
found only 64 (29.5%) icteric. In the studi
recorded by Armas-Cruz et al. 30 per ce
had normal values for serum bilirubin
death.

The clinical significance of jaundice
patients with cirrhosis has not been popular
understood. The gravity of this sign is show
by an analysis of the duration of life aft
the onset of jaundice in 245 patients[148] (Fi
126). Of these, 44 per cent lived 6 month
26 per cent lived one year; and 23 per ce
lived 2 years after the onset of jaundice.

The mechanism of jaundice in Laenne
cirrhosis is not established. However, wh
one considers the vast structural changes,
is to be wondered that jaundice is no mo
frequent or intense. The chief causes appe
to be functional derangement of the liv
cells, and compression of bile ducts by co
nective tissue overgrowth. Also, it has be
suggested that superimposed hepatitis
necrosis may account for the intense jau
dice that sometimes appears terminally,

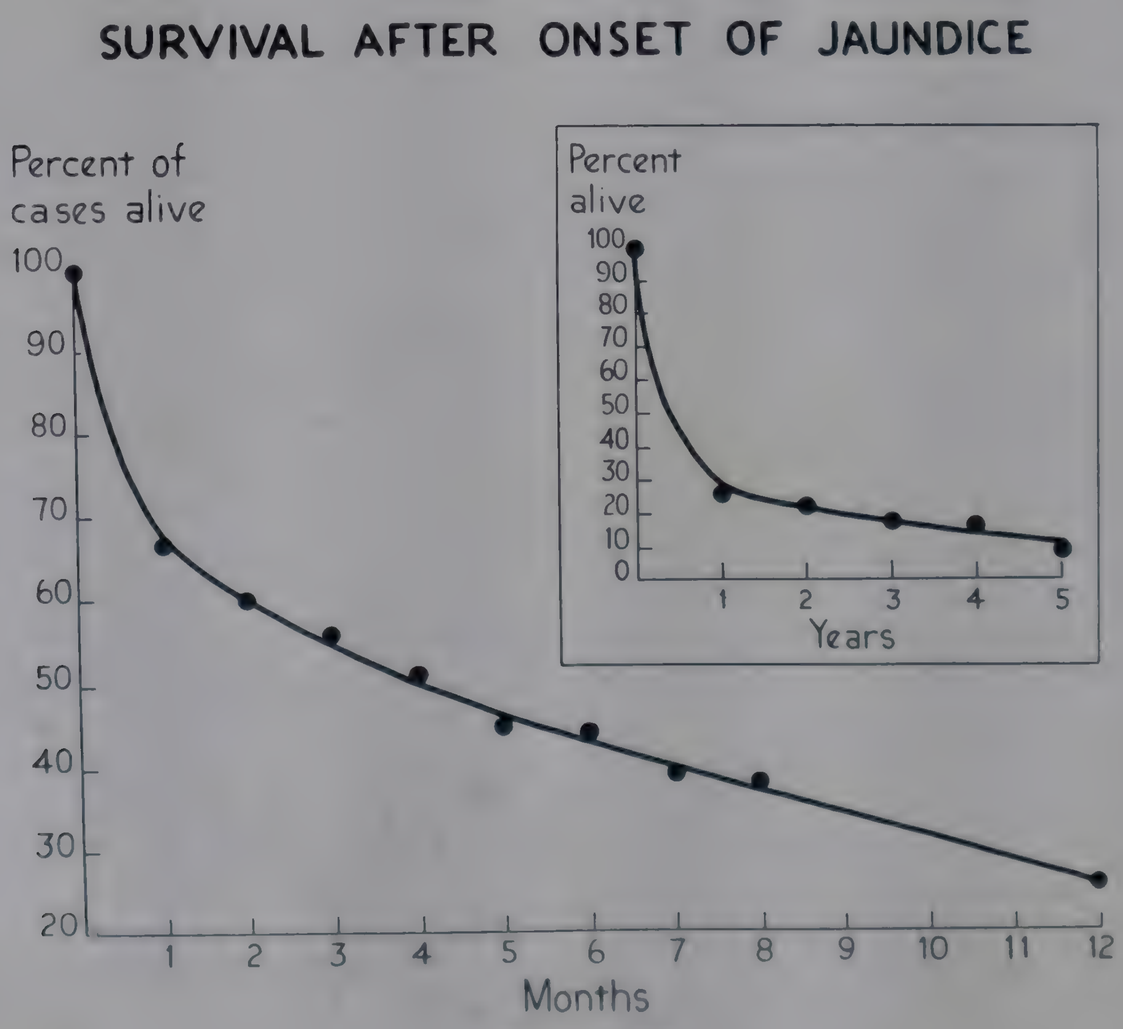

FIGURE 126

there is little evidence to support this point of view.[129, 148] Studies of autopsied cases show little or no correlation between the presence of jaundice and necrosis.

Hepatomegaly. The liver is palpable in about 75 per cent of the patients. In addition to the size of the liver, palpability depends upon increased hardness and possibly some degree of downward displacement of the organ, as well as thinness and relaxation of the abdominal wall. Indeed, small livers are occasionally palpable. Foxwell in 1896[55] pointed out that the liver might be felt without being above average weight. Eppinger[45] noted that the liver was palpable in 80 per cent of his series but enlarged in only 50 per cent on pathologic examination. Ratnoff and Patek[148] found only a rough correlation between palpability and size of the liver. The average weight of 73 palpable livers showing cirrhosis was 1,820 Gm., the weights ranging from 695 to 5,100 Gm. In 30 nonpalpable livers with cirrhosis the average weight was 1,370 Gm., the weights ranging from 570 to 2,920 Gm. Similar findings are reported by others.[2]

It is commonly believed that the liver enlarges early in the disease and later decreases in size with progression of the disease; that at first it is hypertrophic and later atrophic. There is little evidence to support this opinion. It should be pointed out that the liver also appears to decrease in size with recovery from the disease. At times very rapid shrinking is observed, which suggests that palpability is related to edema and fatty changes as well as to increased density from fibrosis.

Splenomegaly. The spleen is found to be enlarged on physical examination in from 30 to 50 per cent of patients. At autopsy an enlarged spleen is discovered in 70 to 80 per cent of the cases. This indicates that considerable numbers are overlooked at examination, since the spleen is larger in life than after death.

The demonstration of splenomegaly is important toward establishing the diagnosis of cirrhosis, since it is so constant a feature. Splenomegaly is not encountered in the early, fatty, precirrhotic stage of the disease.[126] When present, it indicates a well-advanced process, for the size of the spleen presumably reflects the height and the duration of portal vein hypertension caused by fibrosis (cf. the section on pathology).

The spleen appears to vary in size from day to day and may shrink greatly after blood loss. If persistent, repeated search is made, a rewardingly high percentage of palpable spleens is found. In doubtful cases, roentgenography may help to reveal the presence of an enlarged spleen.

Vascular Changes. *Dilated superficial veins,* signs of collateral circulation between the portal and the systemic systems, appear upon the abdomen and the chest in from 25 to 60 per cent of the recorded cases. Like splenomegaly and esophageal varices, they reflect the degree of obstruction in the portal venous system. With infrared photography the extent of the collateral circulation can be detected earlier than with the naked eye. The *caput medusae,* popularly identified with cirrhosis, is a rarity and was seen in only 4 of 386 patients.[148] This grouping of para-umbilical veins is far more characteristic of obstruction to the inferior vena cava than it is of Laennec's cirrhosis. *Venous hum* is heard occasionally over a large umbilical or para-umbilical vein connecting the portal and the systemic venous system.[176, 207]

Hemorrhoids are commonplace in patients with cirrhosis. However, it is questionable that they occur more frequently in cirrhotics than in others of comparable age.

Vascular Spider. One of the most reliable signs of hepatic cirrhosis is the vascular spider, known also as the spider nevus or angioma (Fig. 127). It may be seen in as many as 60 per cent of the patients. The spider is a tiny bright-red arteriole, from which radiate hairlike branches for a distance of about 0.5 to 1.0 cm. The central core pulsates, and this pulsation can be demonstrated by applying counterpressure over the area with a glass slide. On histologic section these vessels resemble small arteries or arterioles, and at times they resemble arterial segments of glomus vessels. For reasons unknown they are seen almost exclusively on the face, the arms and the upper trunk; rarely are they seen over the lower trunk or the legs. In a rough fashion their appearance tends to parallel the course of the disease. They increase in number during failure and they decrease with improvement. Earlier

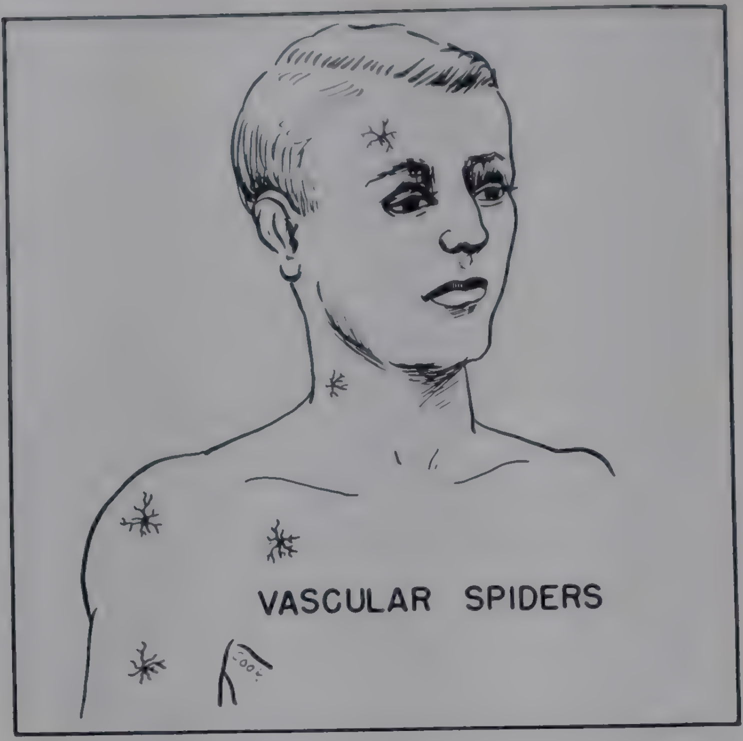

FIG. 127. Extreme example of vascular spiders in a case of hepatic cirrhosis. (Schiff, L.: Clinical Approach to Jaundice, Springfield, Ill., Thomas)

studies[58, 101, 131] have elucidated the arterial nature of these vessels. In a monograph on this subject Bean[8] has suggested that there may be a relation between the vascular spider and the concentration of circulating estrogens or related steroids. He points out that the only other condition in which these are seen with some frequency is pregnancy—especially between the second and the fifth months.

Because of their arterial structure, at times they may give rise to spurting hemorrhage. The writer has observed 3 such instances.

Liver Palms. This condition is characterized by flushed, mottled, reddening of the thenar and the hypothenar eminences and the fingertips. Often it is seen in conjunction with the vascular spiders and doubtless is related to similar vascular changes. However, liver palms are seen in a variety of other conditions (notably rheumatoid arthritis) and in healthy persons.

Herniae. Abdominal herniae are seen frequently in these patients, especially in the presence of ascites. Chapman, Snell, and Rowntree[27, 28] noted that herniae developed in 6 of 58 patients who had cirrhosis without ascites; and that they developed in 47 of 112 patients with ascites. These herniae were umbilical in 24, ventral in 7, inguinal in 9, and epigastric in 2 instances. In case of in pending incarceration, the ascitic fluid shou be removed at once, with the hope of redu ing the hernia. If possible, surgical repa should be deferred until ascites disappear

ESOPHAGEAL AND GASTRIC VARICES

The frequency of these venous dilatatio is doubtless greater than is recognized cli cally. In one study[130] varices occurred in of 124 patients (48%). This included cas of hematemesis, as well as those demo strated at autopsy or by roentgenograph Newer refinements in the use of x-rays doub less will disclose a higher frequency. A occasional esophageal varix is said to occ without portal hypertension and without h patic disease. Such instances must be ra

SEXUAL AND RELATED DISTURBANCES

Impotence in males is commonplace Presumably, this is on an organic basis, sin testicular atrophy and fibrosis frequently a observed at autopsy. Henschen and Bruc reported testicular fibrosis in 16 of 81 ca of Laennec's cirrhosis and atrophy in 8 stances. Other studies[41, 99, 117] confirm t observation. Urinary androgen has be found to be subnormal. Although the changes suggest an organic basis for im tence, it should be borne in mind that t majority of the patients are alcoholics, a that the average age of the males is 50 yea Loss of libido in patients with chronic illn in this age group would not be surprisi Data concerning sterility are not at hand.

Gynecomastia, loss of axillary and pu hair and the appearance of vascular spide commonly seen in cirrhotics,[2, 45, 99, 191] ha been attributed to failure of the damag liver to detoxify estrogens. Assays of ur have shown constant decreases in 17-ket teroids[21] and frequent increases in free a conjugated urinary estrogens.[36, 160] Howev corresponding changes in 17-ketostero and estrogens are found in cirrhotic patie who lack these clinical features. The c relation between the laboratory changes a these physical signs has not been impr sive.[36, 160] It should be added that the val for urinary excretion of hormones may necessarily reflect the concentration of th substances in the blood.

Menstrual Disorders. Corresponding studies for the female are less satisfactory because of the relatively few women of premenopausal age with Laennec's cirrhosis. Both increased and decreased menstrual flow have been described in association with cirrhosis.[148] In our experience[130] decreased or absent menstruation is characteristic; indeed, return of normal menses is a sign of recovery from liver failure. In 66 females with Laennec's cirrhosis Armas-Cruz[2] and his coworkers reported 39 (59%) with amenorrhea. However, it is not clear from their data how many were of premenopausal age. Menorrhagia or metrorrhagia is associated more usually with a generalized bleeding diathesis or with local pelvic pathology. There is little information concerning sexual drive, hormonal changes, or pathologic changes in the ovaries in this group of patients. Pregnancy apparently can occur in the presence of cirrhosis, as reported by Tenney and King.[175]

Hemorrhagic Phenomena

Although several blood-clotting factors may be altered in the presence of Laennec's cirrhosis, a grave bleeding tendency is unusual.

Epistaxis, purpura and gingival bleeding are the manifestations most commonly seen. In childhood and adolescence nosebleeds are experienced by persons who seem to be healthy otherwise. Generally, this tendency is outgrown. However, the appearance of nosebleeds in adult life should suggest the possibility of cirrhosis of the liver, as well as primary blood dyscrasia. In a series of 386 cases[148] there were 70 (18%) with the history of epistaxis and 33 (9%) with purpura; of these 12 had both symptoms. In reviewing 208 cases Armas-Cruz[2] and his associates listed 19.2 per cent with a tendency to epistaxis and purpura. In a series of 124 patients[130] in whom the symptom of epistaxis was inquired into specifically, an ncidence of 40 per cent was obtained. It seems probable that epistaxes are related to ncreased vascularity or to changes in the nasal mucosa, since in most instances there s no generalized bleeding tendency.

Purpura and gingival bleeding (5 to 10% of the cases) are seen more often with advanced hepatic disease and with changes in the blood-clotting factors than is the case with epistaxis. Fagin and Thompson[48] observed this tendency only in jaundiced patients. The rare occurrence of hematuria and melena from multiple bleeding points in the intestine also is associated with advanced hepatic failure.

Decreased concentration of prothrombin[7] and of accelerator globulin,[66] altered fibrinogen[202] and thrombocytopenia[116, 206] have been reported in cases of cirrhosis. Whether or not these changes account for the bleeding phenomena is not established. The correlation between bleeding phenomena and the prothrombin time does not appear to be sufficiently close to attribute the symptoms to decreased concentration of prothrombin alone. In the presence of cirrhosis the administration of vitamin K brings about slight, if any, increase in the concentration of prothrombin.[137]

Anemia

Anemia is common in Laennec's cirrhosis. The degree of anemia bears only a poor correlation with the severity of the disease. The characteristic type is either macrocytic or normocytic, the red blood cells showing little variation in size and shape. In 23 cases of Laennec's cirrhosis Wintrobe[205] found 8 to be macrocytic, 11 normocytic, and 4 hypochromic microcytic. Jarrold and Vilter[77] reported anemia in 24 of 30 cases of cirrhosis, of which 20 had macrocytic and 4 had normocytic anemia. Rosenberg and Walters[157] described findings in 48 cases of cirrhosis (45 portal; 3 biliary). The average mean corpuscular volume was 110 cubic microns; the average red blood count, 3.26 million; the average hemoglobin, 12.0 Gm.

Reticulocytosis varying from 2 to 15 per cent has been reported in these cases. However, red cell fragility tests do not show increased hemolysis to hypotonic saline, nor is the fecal urobilinogen increased.

Characteristically, the bone marrow is normoblastic (not megaloblastic) and shows hyperactivity with extension of red marrow into the shafts of the femur.[10]

The anemia does not respond to the administration of folic acid or liver extract but shows gradual improvement with recovery from the underlying disease. Schiff[162] and his associates demonstrated the presence of antianemic substance (against pernicious anemia) in livers of patients who died from hepatic cirrhosis with macrocytic anemia. Therefore, the anemia does not appear to be due to lack of storage of antianemic principle.

There are occasional cases of macrocytic anemia, associated with megaloblastic bone marrow, and in them a brisk response to liver therapy has occurred. Such instances are interpreted as due to associated deficiency of extrinsic factor or addinsonian pernicious anemia.

The mechanism responsible for the anemia of cirrhosis is not understood. Speculation at present is concerned chiefly over whether or not this represents a hemolytic process.[10, 68]

LABORATORY CHANGES

Characteristic changes in laboratory tests are shown in Table 29. The table indicates findings usually encountered in *advanced* Laennec's cirrhosis. For the most part the tests in common use are of diagnostic value, reflecting the presence or the absence of hepatic damage, but they do not provide an index to the type or the extent of injury. As diagnostic tests the bromsulphalein dye test and cephalin flocculation reaction are probably the most sensitive and dependable of those listed. In following the course of the disease serial values for serum albumin and serum cholesterol ester have shown a fa degree of correlation between the clinical an the laboratory changes.

For a fuller discussion of function tests th reader is referred to Chapter 5.

TREATMENT

Rest

Emphasis is placed upon rest, nutritio diet, and supportive measures. By the tin the patient accepts hospitalization he is us ally weak, mentally dulled, distended wi ascites, and agreeable to rest in bed. Wi improvement he asks for more freedom, a since convalescence may involve ma months, it is not feasible to enforce bed re indefinitely. For those who are in modera failure bed rest for at least half the day advocated. Resumption of activity is allow gradually as jaundice, fever and ascites su side. It is better to prescribe a program th is likely to be accepted than one which too demanding and sooner or later will be jected. However, this point of view does apply to the problem of alcoholism. All frequently patients return to their old hab undoing in a few weeks the improvem that they made in many months. Th should be no compromise with the pati with regard to alcohol, for he seldom is a to restrict his intake within reasona bounds. This is emphasized because ma doctors are too indulgent in treating fundamental aspect of therapy.

TABLE 29. CHARACTERISTIC LABORATORY CHANGES IN ADVANCED LAENNEC'S CIRRHOSIS

Serum albumin	Decreased (especially in presence of ascites)
Serum globulin	Increased
Cephalin flocculation	Positive (2 to 4+) in about 75% of cases
Thymol turbidity	Increased in about 50% of cases
Bromosulphalein dye retention	Increased in over 90% of cases
Serum bilirubin	Increased slightly
Urine urobilinogen	Increased
Serum alkaline phosphatase	Normal or moderate increase
Serum cholesterol total	Normal
Serum cholesterol ester	Decreased
Prothrombin time	Increased slightly
Serum cholinesterase	Decreased
Erythrocyte sedimentation rate	Increased
White blood count	Normal or moderately increased
Nonprotein nitrogen	Normal (increased in cholemia)

DIET

In former years the American diet for paients with cirrhosis of the liver was high in arbohydrate and severely restricted in fat nd protein. In the light of experimental vork during the past 15 years this regimen vas not rational. Indeed, cirrhosis of the iver can be produced in the laboratory animal by means of diets high in carbohydrate, ow in protein, and low in fat (cf. Chap. 4). The diet now in common use contains a generous amount of protein and carbohydrate foods, and it includes meat, milk, eggs, ruit and green vegetables. Some authorities till prefer to restrict fat, but the majority of ecent reports advise a moderate intake of at. In the writer's opinion, restriction of fat enders the diet less palatable and thus curails the food intake. A standard diet employed at the Columbia Research Division, Goldwater Memorial Hospital, Welfare sland, provides 365 Gm. of carbohydrate; 115 Gm. of protein; 175 Gm. of fat. Eggs are served at breakfast; meat, fish, or poultry are served at both dinner and supper; milk s served 3 times with meals, and twice beween meals with 25 Gm. of brewer's yeast powder, in the form of a milk nog. (The yeast, being 50% protein, brings the total protein intake to 140 Gm.) If the paient eats these foods, considered as basic, he remainder of the diet is largely a matter f choice.

For edentulous patients particular care must be taken to supply puréed foods. Small requent feedings are desirable for those who are distended with gas or ascites. Stuporous patients may be fed semiliquid diet by nasal ube. A formula suggested by Smith, Wollaeger, and Victor[170] for this purpose is shown in Table 30.

TABLE 30. TUBE FEEDING FORMULA[170]

Milk, whole	1000 Gm.
Skim milk powder	90
Eggs, whole	200
Dextrimaltose No. 1	100
Cream, 20%	200
Salt	3.0
Supplement containing Vitamin B complex + ascorbic acid	
Total volume	1,500 cc.
Total calories	2150

Since these patients often show signs of multiple deficiencies, supplements of brewer's yeast or of liquid vitamin B complex preparations have been employed. Thiamin chloride (5 mg.) is fed daily, and liver extract (5 cc.) is injected intramuscularly once weekly. If severe polyneuritis, mental confusion or pellagroid changes are present, thiamin hydrochloride (100 mg.) and nicotinamide (300 mg.) are administered daily parenterally. There is no evidence that these supplements are effective in Laennec's cirrhosis uncomplicated by vitamin B deficiencies.

CONTROL OF ASCITES

The control of ascites presents a special problem. Fluids are allowed up to 2,000 cc. daily or up to 2,500 cc. in hot weather. Salt is moderately restricted by excluding its use in the preparation of food or on the tray. Abdominal fluid is tapped before distention interferes with adequate rest or intake of food. Mercurophylline injections (2 cc.) are given once or twice weekly, combined with daily oral administration of 4 to 6 Gm. of ammonium chloride in enteric coated pills. The latter pills are given for 3 or 4 days of each week, and they are omitted in patients who are drowsy or mentally dulled. Although toxic effects of ammonium salts have been described[135] in patients with advanced cirrhosis, the writer has encountered these untoward effects in only a very few patients.

For patients who are hospitalized shortly after the onset of ascites or have only moderate ascites the above measures usually suffice. In the case of stubbornly recurrent ascites more drastic restriction of sodium is helpful toward speedy resorption of ascites, as advocated by workers at the Rockefeller hospital[48] and Boston City hospital.[51] In devising appropriate diets certain milk derivatives rendered free of sodium have been invaluable for maintaining a high intake of protein. Rarely, patients are not tolerant of rigid sodium restriction and they show signs of its lack, with profound weakness, muscular cramps and anorexia. These signs are prone to occur after abdominal taps when a large amount of sodium is removed. In such patients a larger intake of sodium may be necessary, especially at the time of paracentesis.[123]

TREATMENT OF CHOLEMIA

The treatment of cholemia is unsatisfactory. Only rarely do patients recover for more than a few days from this state. Cholemia may be the terminal stage of progressive hepatic failure; it may appear abruptly in the course of intercurrent infection; it may accompany or follow esophageal hemorrhage; it may follow the administration of opiates.[48, 121] The outcome depends in large measure upon the precipitating conditions.[121]

Tube feeding is indicated in such patients unless there has been recent hemorrhage from esophageal varices. In addition, slow intravenous infusion of 10 per cent dextrose totaling 1 to 2 liters and of normal saline totaling 1 liter may be given in 24 hours. To each liter thiamin hydrochloride 100 mg., nicotinamide 300 mg., and riboflavin 100 mg. may be added. The intravenous medication alone has little nutritive value and is not a substitute for oral feeding. However, occasional patients appear to have been revived by this therapy.[180, 171a] Karl and his coworkers have suggested the trial of amino acids and glucose infusions, together with prophylactic "coverage" by chlortetracycline. In the writer's opinion many patients are overtreated at such times. The variety of agents employed must throw the disordered liver into a state of metabolic confusion. The subject of hepatic coma is treated more fully in Chapter 9.

TREATMENT OF INTERCURRENT INFECTIONS

Intercurrent infections formerly accounted for about 25 per cent of the deaths from cirrhosis. With the advent of sulfonamides and antibiotics the dangers from infection have been decreased sharply. Although instances have been cited of hepatic damage produced by sulfonamide drugs, the risk would seem to be justified when continued infection is the alternative. In this regard our experiences[180] confirm that of Peterson and his co-workers.[134] However, since hepatic complications have not been described as the result of treatment with penicillin and other
antibiotics, these agents are generally
preferred.

TREATMENT OF HEMATEMESIS

For the care of hematemesis, trans
of whole blood should be performed a
as possible, since delay may result in
versible shock or coma. Transfusions
be continued as long as there is evide
bleeding. The patient should be sedate
lightly, since he has a tendency to laps
cholemia. The use of esophageal tamp
and the various surgical measures av
for these emergencies are described in
ter 8, "Portal Hypertension."

SPECIFIC ADJUVANTS

Choline and Methionine. Althoug
line and methionine prevent experimen
tritional cirrhosis in the rat, there is le
dence that they are effective in the rep
process after cirrhosis has been pro
Dietary protein (apart from its cont
methionine) and probably other nu
appear to play an important role in
of nutritional cirrhosis.[64, 136]

In dealing with the human disease,
conditions are far less susceptible to c
it has been difficult to assess the v
lipotropic substances.[88, 127, 190] For th
part patients have received highly nu
diets as well as supplementary chol
methionine. Beneficial effects have
measured by function tests and by se
opsies of the liver. Comparisons wi
experience and with other series o
have suggested that improvement w
result of "lipotropic" therapy.[7, 22, 36]
In the experience of others[40, 88, 130, 1]
therapeutic effect has been unimpress
it has been pointed out that the fat
rhotic liver responds as favorably to
and normal hospital diet as it does t
ment with choline and methionine. T
mal hospital diet, to be sure, is far s
nutritionally to the usual diet of th
holic, and possibly it may contain
amounts of choline or methionine. T
of promise for these adjuvants woul
to be in the precirrhotic, fatty stage
disease where they may help prevent

e. There are no harmful effects from
ubstances administered in moderate
.

nan Serum Albumin Solution. Con-
opinions have been expressed con-
g the value of administering intra-
ly concentrated human serum albumin
n. Kunkel and his associates[92] made
on 17 patients with severe hepatic
. In 14 of 15 patients ascites dis-
ed soon following therapy. Patients
ther postnecrotic or Laennec's cirrho-
ponded. The improved nutrition and
l status suggested positive benefit from
erapy. Post and his co-workers[144] ob-
34 patients critically ill with hepatic
is. Here, too, substantial benefit was
ted to treatment with intravenous
n solution. Nine of 16 patients re-
d from coma, an unusually high in-
e. In contrast, Faloon and his co-
s[59] were unimpressed by this form of
tion. Only 4 of 20 patients experi-
a prompt diuresis that could be attrib-
o therapy. In several instances eso-
l hemorrhage occurred within a short time of therapy. Pulmonary edema, due to rapid expansion of plasma volume, also is a hazard in patients who have decreased cardiac reserve.

In the writer's opinion there is a place for treatment with concentrated human serum albumin, not so much for its effect upon ascites formation (as was hoped originally) but as an available and utilizable form of plasma protein. In patients who are critically ill, whose serum albumin is much reduced, this would seem to be a rational form of therapy. Untoward reactions are infrequent if repeated small doses (25 Gm. or less) are administered slowly intravenously.

Intravenous Liver Extract. In certain cases of cirrhosis there is profound anorexia. The patient cannot or will not eat the prescribed diet. Under these conditions a trial of intravenous liver extract may be helpful, as advocated by Labby,[96] Ralli[145] and their co-workers. Stimulation of the appetite (for reasons unknown) may be considerable. There seems to be less indication for this form of therapy in patients whose intake is adequate.

Amino-acid Hydrolysates. In the past these substances were tolerated poorly. Newer preparations seem to provoke relatively few side reactions. Patients with cirrhosis have been maintained in positive nitrogen balance with these hydrolysates as the

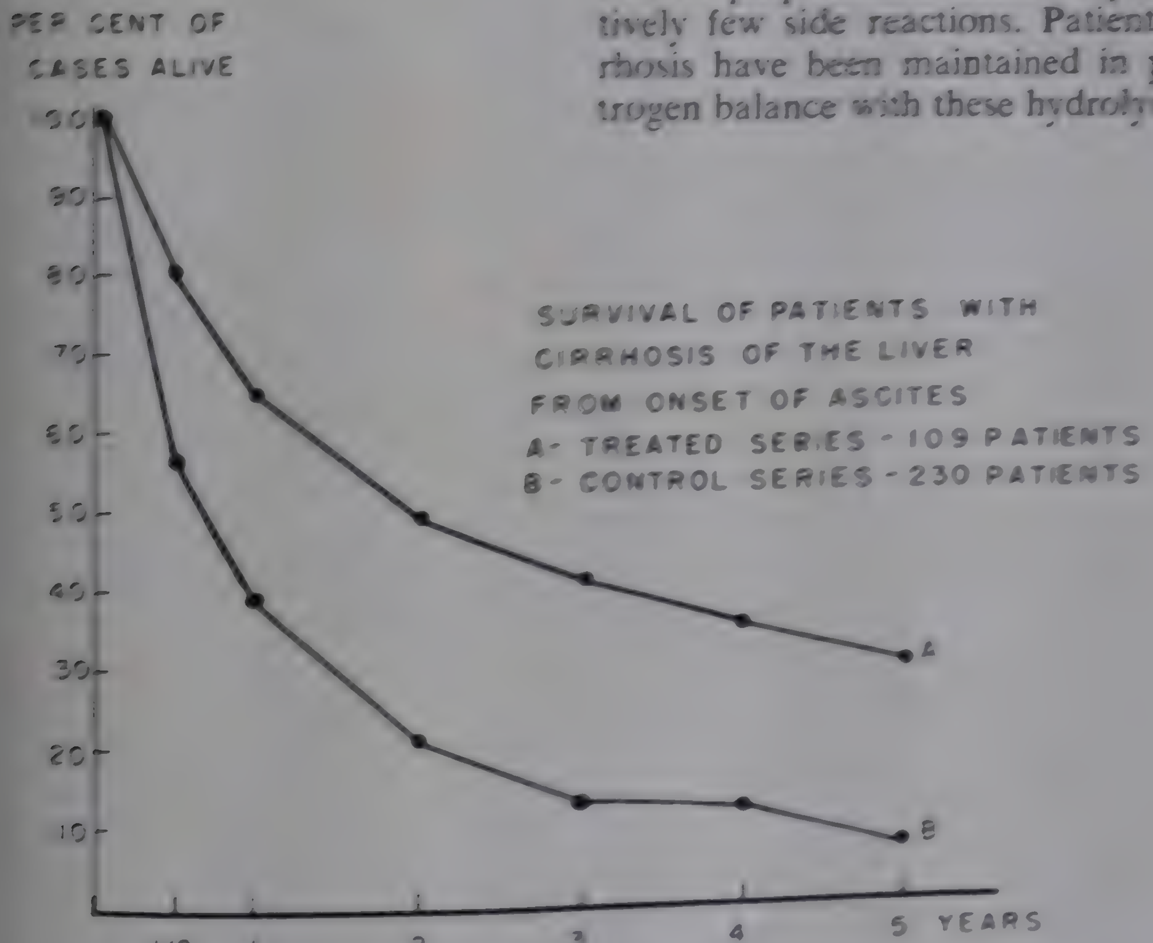

FIGURE 128

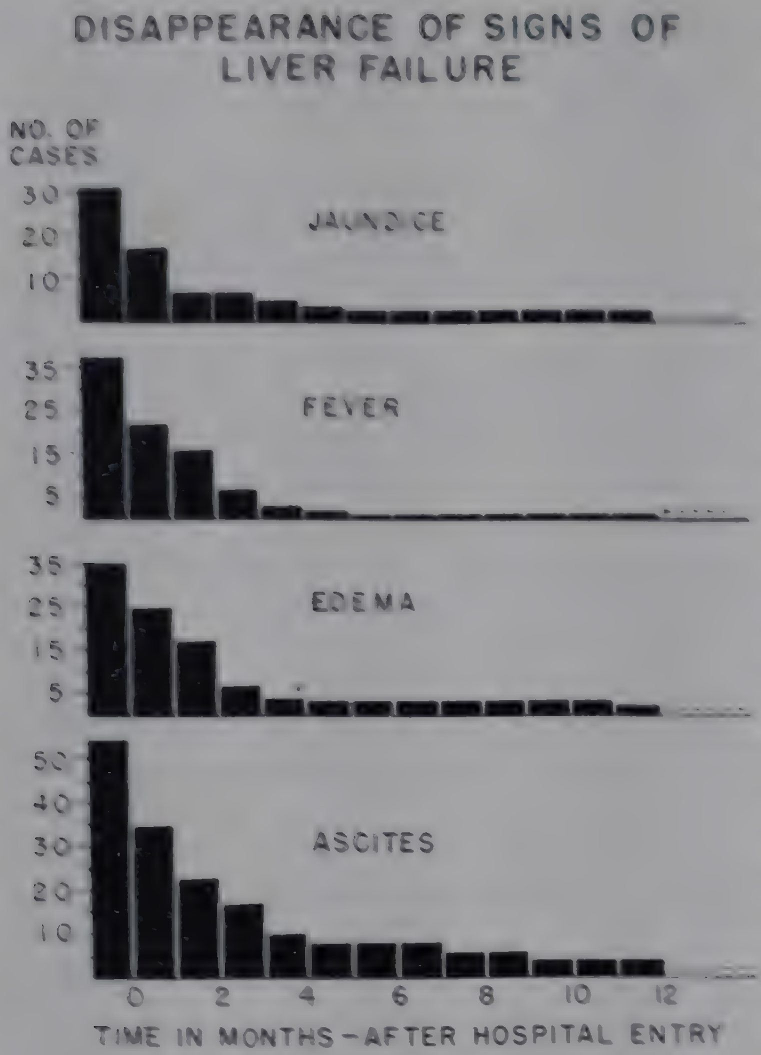

FIGURE 129

chief source of protein. Although some preliminary studies[39, 49, 115] have been favorable, further work is needed before their place is established.

Cortisone and ACTH. The experience with these drugs has been too limited, and the reports are too varied to permit a fair appraisal at this time. In severe viral hepatitis these drugs occasionally exert a dramatically favorable reaction. Likewise, in severe, fatty cirrhosis in which the course may be fulminating[83] these drugs at times have been very effective. In both conditions it is likely that considerable necrosis and acute inflammation are present. There is less evidence to suggest that these agents will be helpful for more chronic stages of cirrhosis.[20]

RESULTS OF TREATMENT: PROGNOSIS

The outlook for patients with Laennec's cirrhosis has improved considerably in recent years. This is shown statistically by comparing periods of survival in the years 1937 to
1947 with corresponding experienc
1916 to 1938. Figure 128 illustrates
riod of survival after the onset of asc
an index of liver failure) in 2 seri
upper line A refers to patients treatec
nutritious diet (rich in protein) ar
longed hospitalization. The lower lin
fers to the control series, also hospital
for lesser periods of time. The stand
for hepatic disease during 1916 to 19
high in carbohydrate and low in prot
fat. The more favorable course of th
series doubtless is due not only to diet
tors and bed rest but also to more
measures to combat infection and
shock from hemorrhage. The experi
other clinics[16, 54, 74, 145, 196] has been
eral agreement with these findings.

The outcome depends greatly u
stage of the disease at which treat
started. At an early stage it is pos
achieve fairly complete clinical and h
recovery. Results are much less sati
in those with advanced hepatic failu
group reported by the writer and
workers 61 of 124 patients (roughly
made sustained significant impro
These results were possible only be
long-continued hospitalization and
care. Figure 129 shows the length
from the beginning of therapy to th
pearance of certain signs of hepatic f
the 61 patients who made signific
provement. Although there is individ
ation, jaundice and fever tend to d
more rapidly than ascites and ed
about 75 per cent of the cases these
disappeared within 3 months. In a f
it took from 6 to 12 months to ac
this end. Gain in weight and stren
sidence of epistaxis, return of men
improved laboratory functions acco
these changes.

In general, there was considerabl
fore the laboratory tests reflected
changes. Certain tests, such as the
phalein dye test, may remain abno
years despite sustained clinical impr
In 40 of 61 patients there was decrea
retention; in 21 cases the cephalin
tion test became negative; in all ca
was increase of serum albumin. T

r serum albumin before therapy was 100 cc., and after treatment it was per 100 cc. In our experience and others[2, 128] serial values for serum al- ave corresponded fairly closely to the changes and thus have served as a uide to prognosis. In other hands the holesterol ester[155] has been of similar .

OLOGIC CHANGES WITH CLINICAL IMPROVEMENT

e is a poor correlation between the or functional changes in Laennec's s and the histologic findings obtained y of the liver or at autopsy.[86, 141, 151] disappears from the liver several after the institution of an adequate anges in size, shape and staining qual- e liver cells, changes in inflammatory reaction, and particularly in connec- ue response are unpredictable. In cer- es there appears to be regression at the more acute changes, whereas in ramatic clinical improvement may be d with little alteration of histologic e. However, it should be stated that disagreement on this point, some ob- reporting a closer correlation between and pathologic changes.[179, 180, 193]

LICATIONS AND ASSOCIATED CONDITIONS

current infections are frequent, and re a serious threat to life prior to the ction of antibiotics. Table 31 lists the ns most commonly seen in a series of 386 patients.[148] Similar data have been recorded by others.[97, 108, 154]

1. INTERCURRENT INFECTIONS IN 386 ENTS WITH LAENNEC'S CIRRHOSIS[148]

	NUMBER
pneumonia	17
erculous peritonitis	12
neumonia	5
nia	4
as	3
s	3
lous peritonitis	2
phritis	2
neous	8

In former years tuberculosis was a common complication. Rolleston and McNee[154] state that "in about 12 to 14 per cent of cases with cirrhosis death is directly due to pulmonary tuberculosis," and this apparently was the usual experience at the turn of the century. Blumenau[14] reported that of 126 autopsied patients with cirrhosis 10 per cent died of tuberculosis. However, in the series listed above tuberculosis was present clinically in only 4 of 386 patients. Two had tuberculous peritonitis.

In addition to the listed infections phlegmonous enteritis is encountered in a significant number of cases, apparently intervening shortly before death. This has been observed also in cases of acute yellow atrophy, and it is not specific for Laennec's cirrhosis.

Glomerulonephritis as an associated condition was found in 7 per cent of 200 cases of cirrhosis.[132] Both acute and chronic forms were encountered. The pathologic lesions were those of intracapillary glomerulonephritis. Since the usual incidence of glomerulonephritis does not exceed 1 per cent of the hospital population, this association appears to be significant.

Peptic Ulcer. The coincidence of peptic ulcer and cirrhosis of the liver has been mentioned by several observers.[144, 184] Incidences varying from 1.8 to 19.5 per cent have been recorded. In this country the usual range has been from 5 to 10 per cent of autopsied cases. Whether or not this is a statistically important group, whether it exceeds the number expected for this age and sex has not been settled.[44] In practice it is well to bear this complication in mind, since hematemesis in patients with cirrhosis at times arises from peptic ulcer rather than esophageal varix.

Thrombosis of the Portal Vein. This relatively rare condition is encountered in roughly 2 per cent of the cases of cirrhosis. When thrombosis is partial there are few distinguishing symptoms. With sudden closure of the vein more severe symptoms occur, such as shock, hematemesis, paralytic ileus, rapid onset of ascites and cholemia. Under these circumstances the condition should be suspected.

Primary Carcinoma of the Liver. In about 4 per cent of the cases of "portal" cirrhosis a superimposed malignant hepatoma is found at autopsy. This condition generally is not discovered during the life of the patient, since there may be few if any diagnostic clues. For a full discussion of the subject the reader is referred to Chapter 21.

Causes of Death. It has been pointed out that death in Laennec's cirrhosis occurs more frequently from complications of the disease than from "pure" cholemia. In several series of cases[2, 4, 25, 38, 47, 121, 148] cholemia accounted for 15 to 50 per cent of fatalities, hemorrhage, for 20 to 40 per cent; intercurrent infections, especially pneumonia and peritonitis, for 10 to 25 per cent. Postoperative deaths also were commonplace. They revealed the grave risk of surgery in the presence of hepatic failure. The chief cause of death today undoubtedly is eso
gastric hemorrhage.

KWASHIORKOR

Kwashiorkor (malignant maln
disease or syndrome occurring i
children) is characterized clinic
treme malnutrition and pathol
fatty livers progressing to cirrhos
ease with its variants appears t
wide in distribution and it has b
by various names. It has been mo
in tropical countries, namely C
South America, the West Indies,
ical Africa,[58, 60, 136, 155] India an
Similar types of malnutrition
known in Europe as "starch o
trophy" or *mehlnährschaden*. (S
Liver Diseases in Infancy and Ch

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hapter 15

POSTNECROTIC CIRRHOSIS

Arthur J. Patek, Jr., M.D.

Postnecrotic cirrhosis of the liver has been
riously named "healed or chronic yellow
rophy,"[2] "toxic cirrhosis,"[15] "posthepatitic
rhosis," "multiple nodular hyperplasia,"[16]
d "coarsely nodular cirrhosis." Marchand[16]
s probably the first to delineate this type
m Laennec's or alcoholic cirrhosis. Al-
ugh many workers believe that clinical
d pathologic distinctions between these
rhoses are not feasible on the basis of
ailable data, the current trend is to regard
stnecrotic cirrhosis as an entity.

PATHOLOGY

The liver appears small and discolored. Its
rface shows depressed areas and large nod-
es of varying size (Fig. 130). At times a
rge portion of a lobe, in particular the left
be, is atrophied. The depressed areas, which
e composed of broad and narrow bands of
nnective tissue containing few if any paren-
ymal cells, probably represent collapsed
oma. The nodules represent proliferating
er cells which lack the orderly arrangement
normal liver tissue. In some areas focal
croses are present. Fatty changes are slight
absent. Frequently, bizarre liver cells are
en. In other portions of the liver the normal
bular structure may be retained.

These findings may be contrasted with
ennec's cirrhosis, in which the liver typi-
lly shows finely diffuse and uniform
anges. Small nodules of liver cells are
rrounded by narrow bands of connective
sue, giving the effect of an orderly arrange-
ent. Bizarre liver cells are uncommon, but
tty changes usually are pronounced.

Intermediate forms of cirrhosis occur
hich make the differentiation almost impos-
ble, as has been pointed out by a group of
pathologists conferring on this subject.[18] In order to show up the differences between these two diseases, Baggenstoss and Stauffer[1] compared 43 fatal cases each of "posthepatitic" cirrhosis and alcoholic cirrhosis. In the first group the clinical data suggested viral hepatitis as the causative agent. Other causes for hepatitis were excluded. The alcoholic group presumably excluded other causes for hepatic damage except for 2 cases with history of viral hepatitis 3 and 9 years previously. In the alcoholic group jaundice occurred in 86 per cent, an unusually high incidence. In their detailed analysis, the authors point out the overlapping that occasionally occurs. In 7 cases of posthepatitic cirrhosis the pathology was similar to Laennec's, and in 4 cases of alcoholic cirrhosis the reverse was true.

In the writer's opinion there is little doubt that certain cases of chronic, progressive hepatitis may lead to diffuse cirrhosis that closely resembles the alcoholic type. However, the reverse situation seems to be less plausible. When the postnecrotic type of cirrhosis occurs in an alcoholic, it seems more likely that the patient had indeed postnecrotic cirrhosis, or a mixed lesion. In 13 of 45 cases[19] with classical pathologic features of postnecrotic cirrhosis there was associated alcoholism.

INCIDENCE

Postnecrotic cirrhosis comprised 8.4 per cent of a series of 550 cases of cirrhosis reported by Mallory.[15] Karsner[13] estimated 10 per cent of his cases of cirrhosis to be of this this group. In 124 cases of cirrhosis reported by the writer[17] 15 (11%) were presumed to be postnecrotic. Of these, 7 were proved at autopsy. In England, where alcoholism is much less frequent than in the past, postnecrotic cirrhosis is becoming relatively more frequent.[14]

AGE AND SEX

All ages are involved. The distribution in Baggenstoss and Stauffer's series[1] ranged from 4 to 77 years, with an average age of 36. Some writers believe that the disease is more prevalent among females, but the total number of reported cases has been too small to establish this point. In one series of 46 cases 63 per cent were males;[15] in another series of 43 cases 60 per cent were females;[1] in a third series of 45 cases 60 per cent were females;[19] in a fourth series of 108 cases reported from Denmark[3] over 95 per cent occurred in women, the large majority of whom we over 45 years of age. This represented a sp cial group of cases, etiology undetermine and for the most part a subacute form of th disease. Since postnecrotic cirrhosis appa ently can follow hepatic injury due to sever different unrelated causes, the wide age di tribution and relatively equal sex inciden (except for the Danish experience) is n surprising.

ETIOLOGY AND PATHOGENESIS

The extensive necrosis of the liver pr duced by infectious hepatitis generally is fo lowed by complete healing. In a small nur ber overwhelming injury leads to death fro acute yellow atrophy. In another small gro

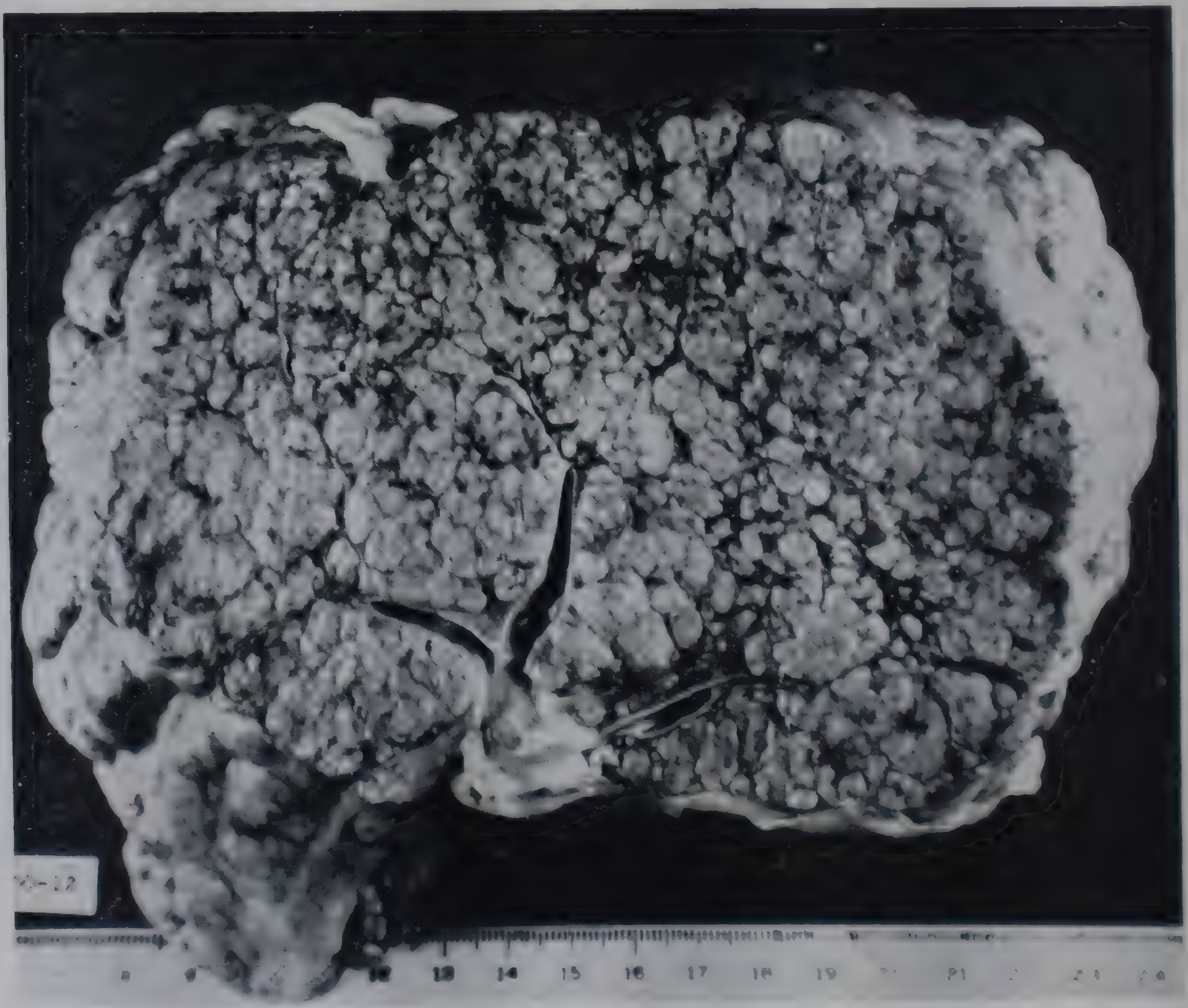


FIG. 130. (A) The coarsely nodular liver exhibits marked variation in pattern and character of nodulation. Of note are the broad trabecularlike bands of connective tissue which course irregularly. (B) A close-up macroscopic view, emphasizing the variable size of the large regenerated nodules and the irregular nature of the scarring. (C) A photomicrograph, revealing the characteristic broad septal scarring. The large parenchymal nodules reveal no pseudolobulation but contain multiple distorted lobules, many portal canals and asymmetrically located central veins.

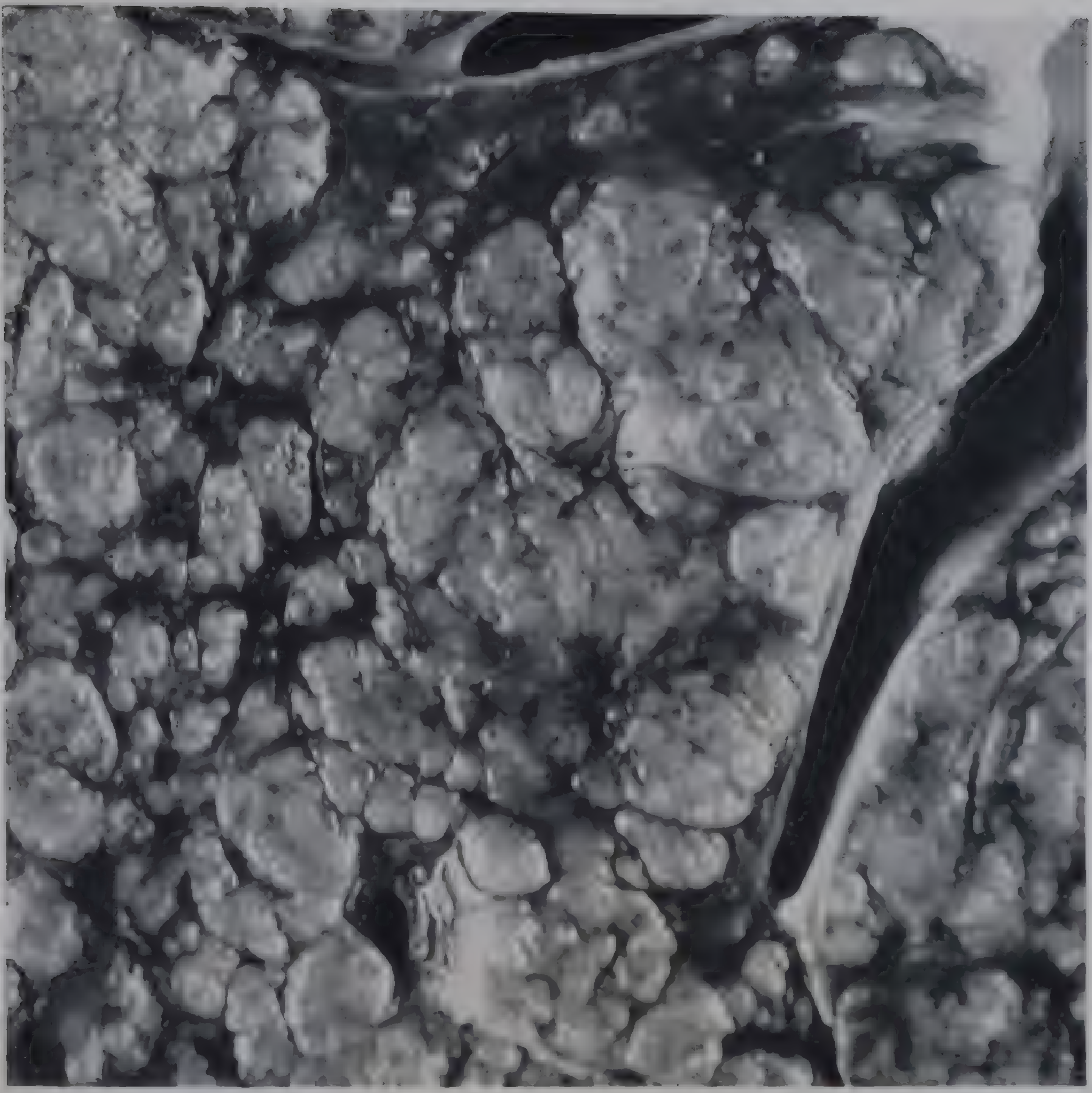
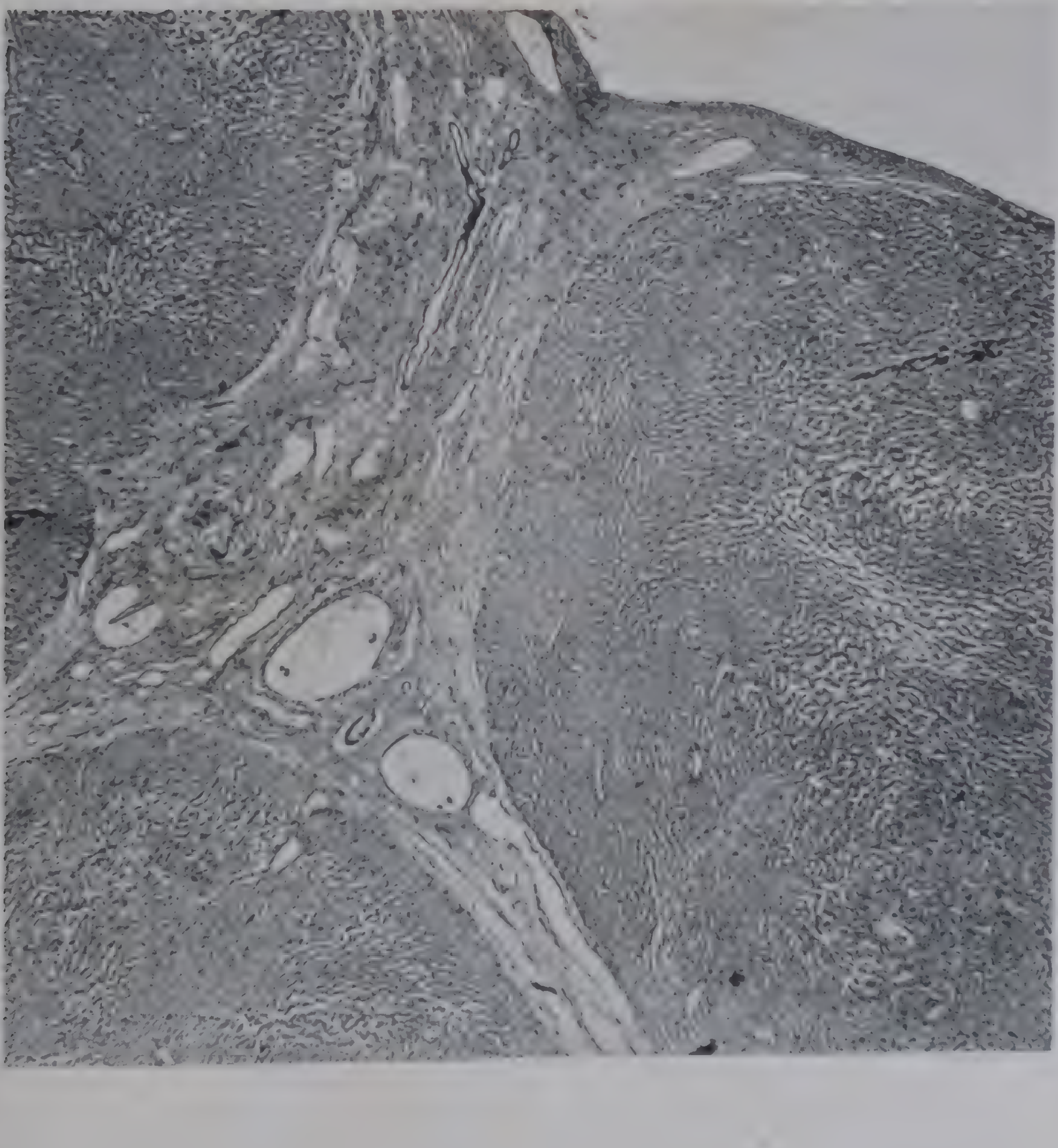


FIGURE 130 (*Contd.*). B (*Top*). C (*Bottom*)



the illness assumes a progressive or intermittent course which produces the pathologic features of postnecrotic cirrhosis.[6] Various hepatotoxins, such as cinchophen, carbon tetrachloride, trinitrotoluene can produce the same clinical-pathologic sequence.[11, 12]

However, there are several puzzling features with regard to antecedent factors in postnecrotic cirrhosis. The intensity of the original hepatitis seems to bear little relation to the later development of cirrhosis. In the majority of cases the original hepatitis has been so mild as to escape detection. Therefore, it seems likely that other conditioning factors are at play. It is possible that constitutional or environmental factors play a role, either in rendering the liver more vulnerable or in activating the hepatotoxic agent.

In recent years the studies of Daft, Sebrell, and Lillie,[5] of Himsworth and Glynn[11] and others[10, 22] have shown the importance of nutrition with reference to experimental necrosis of the liver. Rats, placed on low-protein diets deficient in tocopherol or cystine, develop massive necrosis of the liver. The lesions are prevented by appropriate supplements of tocopherol, cystine, or methionine as a source of cystine. It has not been demonstrated that there is a human counterpart to this experimental disease. It has been suggested[12] that the atypical nodular cirrhosis seen in the African Rand and in the Punjab of India may be analogous lesions. It also is possible that the metabolism of some essential substance, such as cystine or methionine, may be blocked in the course of infectious hepatitis and thus lead to more extensive necrosis. At present one can do no more than speculate about this subject.

TABLE 32. ANTECEDENT FACTORS IN 45 CASES OF POSTNECROTIC CIRRHOSIS

Past history (5 to 12 years) of jaundice or hepatitis	6 patients
Present illness initiated by acute hepatitis	12 patients
Hepatotoxic chemicals (CCl_4; Arsenicals)	8 patients
Chronic alcoholism	13 patients
No apparent contributory factors	12 patients
Malnutrition—data inadequate	

ANTECEDENT FACTORS

In searching for factors that might bear
the etiology of the disease, a series of
cases was analyzed.[19] It is clear from Tal
32 that etiologic factors are unknown in o
fourth of these cases. In others, there was t
history of hepatitis or of an illness that clos
resembled infectious hepatitis. It is possil
that the 12 cases without histories of hepati
may have had the disease in latent form. T
incidence of alcoholism is high, suggesti
that alcoholism may possibly render the li
more vulnerable to infectious hepatitis, as
apparently does to chemicals such as carb
tetrachloride.

SYMPTOMATOLOGY

The chief symptoms and signs of the d
ease, as observed in a series of 45 cases,[19]
shown in Tables 33 and 34. Their incider
is compared with similar data obtained i
series of Laennec's cirrhosis.

The onset in 12 instances of postnecr
cirrhosis resembled acute viral hepatitis w
malaise, anorexia, nausea, vomiting, abdc
inal distress, jaundice, light colored sto
and dark urine. This syndrome is decidedly
variance with Laennec's cirrhosis, in wh
this stormy onset would be unusual. In ot
patients, however, the illness began gra
ally, and the initial symptoms provided
clue to the type of cirrhosis present. I
series of 35 cases, Kelsall, Stewart,
Witts[14] noted that 17 developed the dise
abruptly with an onset like acute hepat
and that 18 developed symptoms gradua

Abdominal pain was a common c
plaint, present in almost 80 per cent of
patients. Except for one patient with pe
ulcer and one with portal vein thromb
the pain apparently was related to the
patic disease. It usually is episodic and
times is associated with jaundice and fe
Occasionally, it is severe, crampy, coli
and may simulate biliary colic.[24]

In addition to abdominal pain, 41 of
patients had one or more symptoms refer
to the gastro-intestinal tract, such as a
rexia, nausea, vomiting, "heart burn" or
arrhea. These symptoms—the abdom
pain and the gastro-intestinal distres

TABLE 33. SYMPTOMS OF POSTNECROTIC CIRRHOSIS IN 45 PATIENTS.[19] COMPARISON WITH LAENNEC'S CIRRHOSIS

SYMPTOMS	NUMBER OF CASES	PER CENT OF CASES	PER CENT OF CASES OF LAENNEC'S CIRRHOSIS[148]
Abdominal pain	35	78	31
Anorexia	26	58	35
Nausea	21	47	33
Weight loss	18	40	53
Hemorrhagic phenomena	18	40	26
Hematemesis	15	33	27
Vomiting	15	33	30
Weakness at or near onset	14	31	21
Diarrhea	13	29	20
Malaise at or near onset	10	22	3
Pruritus	7	16	3
Oligomenorrhea or amenorrhea	7 of 27 ♀	26	7

TABLE 34. PHYSICAL SIGNS OF POSTNECROTIC CIRRHOSIS IN 45 PATIENTS.[19] COMPARISON WITH LAENNEC'S CIRRHOSIS

PHYSICAL SIGNS	NUMBER OF CASES	PER CENT OF CASES	PER CENT OF CASES OF LAENNEC'S CIRRHOSIS[148]
Jaundice	40	89	65
Ascites	40	89	78
Palpable liver	34	76	75
Edema	32*	71	61
Palpable spleen	19	42	44
Fever without apparent cause	18	40	24
Hemorrhoids	15	33	27
Dilated veins	14	31	24
Hydrothorax	12	27	6
Liver breath	11	24	..
Vascular spiders	10	22	..
Acneiform rash	9	20	..
Palmar erythema	7	..	..

* Including 2 patients without ascites. 4 patients before ascites was noted, and 2 patients with nephritis.

eemed to be more pronounced and frequent postnecrotic than in Laennec's cirrhosis. leeding tendencies in the form of epistaxis, ingival bleeding and purpura were frequent this series as well as others.[1, 8, 14]

The physical signs of postnecrotic cirrho- s are similar to those of Laennec's, the dif- erences being qualitative or related to time. alnutrition, for example, is less conspicuous the postnecrotic type; one third of the pa- ents were described as well nourished. Jaundice is an early and persistent sign, and it is apt to be fairly marked in degree. When it is accompanied by clay-colored stools the disease picture may be mistaken for primary biliary cirrhosis. In the latter, higher values for serum cholesterol, alkaline phosphatase and serum lipids are the rule.

Ascites, one of the first signs of hepatic failure in Laennec's cirrhosis, is a relatively late sign in postnecrotic cirrhosis and indicates far-advanced disease. Once it appears

Table 35. Laboratory Findings in 45 Cases of Postnecrotic Cirrhosis.[19] Characteristic Changes

Red blood count	3 to 4 million per cu. mm.
Hemoglobin	9 to 12 Gm. per 100 cc.
Mean corp. volume	100 to 113 cu. mm.
Reticulocytosis	Occasional
Fragility test	Normal
White blood count	Normal
Differential count	Normal (Eosinophils 7 to 14% in 4 patients)
Sedimentation rate	More than 20 mm./hr. in 70%
Serum albumin	Less than 3.0 Gm. in 80%
Serum globulin	More than 4.1 Gm. in 50%
Cephalin flocculation	Positive in over 90%
Thymol turbidity	Positive in over 90%
Bromsulphalein retention	Positive in over 90%
Serum bilirubin	More than 5 mg./100 cc. in 50%
Urine urobilinogen	Increased in over 90%
Stool stercobilinogen	Occasional decrease (7 of 24 patients)
Alkaline phosphatase	Less than 10 B.U. in 10 Between 10 and 19 B.U. in 9 Between 22 and 28 B.U. in 3 (total, 22 patients)

it tends to remain constant. In only 8 of 41 patients with ascites[19] was there a temporary subsidence of this sign.

LABORATORY FINDINGS

Laboratory findings in 45 cases are indicated in Table 35. Here, too, the changes are similar to those encountered in Laennec's cirrhosis but with some qualitative differences. The serum globulin, the serum bilirubin and the alkaline phosphatase tend to be somewhat higher in postnecrotic cirrhosis. According to Watson[23] and Baggenstoss and Stauffer[1] moderate leukocytosis is commonplace in Laennec's but unusual in postnecrotic cirrhosis.

DIAGNOSIS

From the foregoing discussion it is apparent that the diagnosis rests upon clinical and pathologic findings. The criteria are not sharply defined. A typical patient is one in whom signs of progressive liver disease date from an episode of acute hepatitis; in which illness is characterized by jaundice, gastrointestinal distress, lack of response to dietary therapy, and death from cholemia; in which the liver at autopsy exhibits areas of necrosis, broad bands of scar tissue, irregular nodular areas of regeneration, and little or no fa changes.

COMPLICATIONS

The complications encountered rel chiefly to *infection* and *esophageal hem rhage*. In a series of 45 cases[19] infections w frequent; 8 had peritonitis, 8 had pneumor and 5 had phlegmonous enteritis. Chro glomerulonephritis occurred in 3, and pye nephritis in 4 patients. Hematemesis, p sumably from esophageal varices, occur in 33 per cent, as compared with 27 per c of a series with Laennec's cirrhosis (Table 33). Baggenstoss and Stauffer[1] ported hematemesis to be less frequent the postnecrotic group. It is possible that differences are not significant but are rela to the small number of cases involved. T tendency toward hematemesis appears to related to the duration of the disease, presumably to the degree of scarring nodular regeneration that compress the p tal vascular bed. In more acute forms of disease[3] esophageal bleeding is uncomm

TREATMENT

The principles of treatment for pos crotic cirrhosis are the same as those cribed for Laennec's cirrhosis: prolonged ed rest, a well-balanced diet and supportive are. The management of ascites, edema, emorrhage and intercurrent infections has een discussed.

There is a tendency in this disease toward eriodic flare-ups or exacerbations,[4] with aundice, fever, gastro-intestinal symptoms ecoming pronounced. During these epi-odes, which probably signify active inflam-ation, bed rest is most important. At such mes of flare-up the cautious trial of corti-one has been helpful in the writer's limited xperience. The place of this drug in the erapy of hepatitis and cirrhosis is not yet stablished. Both favorable[7, 21] and unfavor-ble[5] reports have appeared.

PROGNOSIS

The natural history of the disease is not fully known. Doubtless, there are many patients with lesser grades of the disease who recover completely. Even advanced postnecrotic cirrhosis may heal sufficiently to allow fairly normal life, since unsuspected latent cases are discovered at autopsy. However, the general outlook is grave in those patients who exhibit signs of hepatic failure. Although there may be short remissions from jaundice or ascites, a slowly progressive downhill course is the rule. In a group of 45 patients[19] 64 per cent were alive 1 year after the onset of failure, and only 22 per cent survived 5 years. The chief causes of death are cholemia and esophageal hemorrhage.[1, 19, 24]

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hapter 16

BILIARY CIRRHOSIS

Henry G. Kunkel, M.D.

Biliary cirrhosis can be separated readily ito two major groups: the primary type reulting from a disturbance within the liver ivolving the smaller bile channels, and the econdary type resulting from an obstructive rocess in the extrahepatic bile passages. In oth types the pathologic disturbance is hronic in nature, resulting in the gradual evelopment of cirrhosis. The exact mechaism by which cirrhosis develops is not comletely clear in either case. It appears to be more straightforward process in the secondry type where the obstructive lesion in the xtrahepatic ducts results in a backing-up of ile with dilatation of the large and the small ucts proximal to the liver. Then, secondary nflammation around the dilated channels ithin the liver may lead to the development f cirrhosis. Although a similar process may lso be involved in primary biliary cirrhosis ith obstruction further up the biliary system n the cholangioles, it appears more likely hat in the majority of cases there is regurgiation of bile by leakage through injured bile hannels. Here the pathologic process leading the involvement of the cholangioles or ther bile radicles may produce the cirrhosis irectly.

In either type the biliary system is involved n a somewhat selective manner, and the prinary clinical and laboratory manifestations f the illness are those of chronic biliary obtruction, at least in the early stages of the isease. One of the manifestations of the iliary obstruction in both types of biliary irrhosis is an elevation of the cholesterol nd phospholipid levels of the serum. This nay be extreme and prolonged and leads to ne development of xanthomatosis in some ndividuals with both the primary and the econdary types. Thus, it is now generally agreed that xanthomatous biliary cirrhosis does not represent a separate disease entity but simply an extreme picture of the two types of biliary cirrhosis.

Many different pathologic processes can give rise to each type of biliary cirrhosis. In the case of the secondary type such things as common-duct stone, postoperative bile-duct stricture, various carcinomas, hydatid cysts and congenital bile-duct atresia have been demonstrated as causative agents. In the primary type a special sensitivity to arsenicals, hemochromatosis and occasionally infectious hepatitis appear to be implicated in the causation of the intrahepatic bile channel disturbance. However, in the vast majority of patients with primary biliary cirrhosis the causative agent is unknown. Multiple undetermined agents may be responsible for the lesion, but certain clinical and pathologic similarities in this group suggest a common etiology. The most striking feature is the overwhelming predisposition for adult females.

HISTORICAL CONSIDERATIONS

The concept that cirrhosis can develop following prolonged biliary obstruction developed during the latter half of the nineteenth century through the clinical studies of Wyss,[51] Moxon,[37] Fagge,[17] Pye-Smith,[40] Hanot[21] and Mangelsdorf.[33] During the same period Legg[29] and Charcot and Gambault[11] demonstrated similar changes in the liver of experimental animals produced by ligation of the larger extrahepatic bile ducts. Biliary cirrhosis without extrahepatic biliary obstruction was first classified as a separate disease by Hanot[21] in 1875, and the name "Hanot's cirrhosis" was applied by Kiener[26] to similar

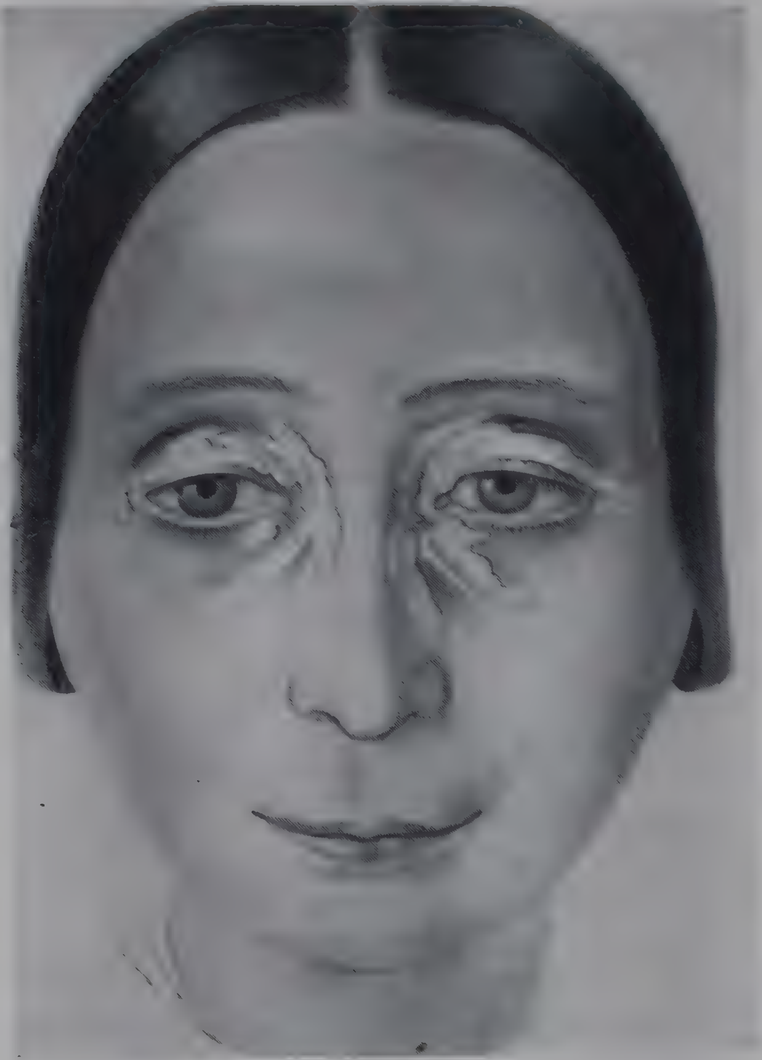

FIG. 131. Jaundiced female with xanthelasma, reproduced from original paper of Addison and Gull. (Addison, T., and Gull, W.: Guy's Hosp. Rep. 7:265)

cases observed primarily in France. This type of cirrhosis appeared to be of infectious origin and often was associated with fever. It occurred primarily in young males and was characterized by inflammation in the portal areas, with involvement of the small bile ducts and secondary cirrhosis. Considerable confusion arose concerning Hanot's cirrhosis, and doubt was raised particularly among English and American workers regarding the existence of such a syndrome. Gradually, new descriptions of conditions similar to primary biliary cirrhosis arose under a wide variety of names: pericholangiolitic biliary cirrhosis, cholangiolitic biliary cirrhosis, cholangitis lenta, chronic intrahepatic obliterating cholangitis, intrahepatic cholangitic biliary cirrhosis, nonobstructive cholangitic biliary cirrhosis and xanthomatous biliary cirrhosis.

An entirely separate field of investigation
centered on biliary cirrhosis associated
xanthomatosis. In 1851 Addison and
presented a classical description of a
of patients with chronic jaundice and
goidea. The latter was their term fo
xanthomatous skin lesion (Fig. 131
number of other similar cases soon app
in the literature, and in 1869 Murchi
demonstrated the lack of involvement
extrahepatic biliary tract in a patient
this syndrome. A review of the literature
1851 to 1950 by Ahrens and co-wor
revealed 92 cases of chronic biliary obs
tion with xanthomatosis. Twelve addit
cases were found in the literature from
to 1953. The reports of Weber[47] in
Futcher[18] in 1905 and Dyke[15] in 1928 c
showed that extrahepatic bile-duct p
ogy, particularly stones, could lead to b
cirrhosis and xanthomatosis. Futcher de
strated disappearance of the xanthomat
jaundice following surgical remova
stones. Several other workers[12, 39] noted
thoma formation of the inner lining c
bile ducts. Thannhauser and Magenda
in 1937, impressed by these reports
noting extremely high levels of chole
and phospholipid in the sera of their pat
felt that the lipid disturbance was a pr
metabolic disease and that the biliary
involvement probably resulted from the
thomatous deposits in the biliary trac
though this hypothesis proved to be w
these workers deserve considerable cre
the classification of xanthomatous bilia
rhosis as a separate syndrome and for
dating the unique and interesting lipid p
in the serum of these patients.

Sporadic case reports,[23, 24] where n
deposits were found in the biliary tract
the liver and where the history of the
suggested primary involvement of the
with the lipid disturbance appearing s
arily, pointed against this viewpoint.
Fuentes, Velasco Suarez and del Cam
1947 presented conclusive evidence
the lipid metabolic disease concept in a
cut description of 6 cases of biliary x
matosis. They stressed the similarity
lipid abnormality in cases clearly d
extrahepatic biliary obstruction and th
the intrahepatic type. MacMahon and T
hauser[34] in 1949, on the basis of an ext

hologic study of 3 cases, recognized a
icholangiolitic chronic inflammatory proc-
leading to biliary cirrhosis as the primary
ormality leading to the xanthomatosis.
ey pointed out the specific nature of the
hologic process in the early stages fol-
ed by a more nonspecific biliary cirrhosis
r on. Dauphinee and Sinclair[14] in 1949
orted 10 cases of primary biliary cirrhosis,
f which developed xanthomatosis. They
not consider the xanthomatous type a
arate disease entity. Ahrens and co-work-
collected 24 proved cases of chronic
rahepatic biliary obstruction with xan-
matosis from the literature prior to 1950
added 2 cases of their own. They empha-
d the similarity of the sequence of events
ding to xanthomatosis in this group and
those with intrahepatic biliary involve-
nt. A similar serum lipid picture with the
nary abnormality in phospholipid and
cholesterol always was observed. They
ssed the point that, as in secondary biliary
hosis, many patients do not develop xan-
matosis; thus also in primary biliary cir-
sis a number of cases are found who do
develop skin deposits. In each situation
xanthomatous complication depends on
degree and the duration of the lipid
ormality in the serum.

Ricketts and Wissler[41] have reported re-
tly 9 well-studied cases of primary biliary
hosis, only 2 of which developed severe
d changes in the serum and xanthoma-
is. They found similar changes in the liver
both groups. No etiologic factor was evi-
nt in any of their cases. Shay and co-work-
[42] furnished further data on the similarity
ween the primary and the secondary types
biliary cirrhosis. However, these authors
d to the older view that the elevated cho-
terol acts as an "irritant that stimulates
production of fibrous tissue around the
r cholangioles."

Although considerable attention was fo-
ed on the xanthomatous type of biliary
hosis, important information accumulated
arding specific etiologic factors in certain
es of primary biliary cirrhosis. Hanger
Gutman[20] in 1940 described a clinical
ture resembling obstructive jaundice that
urred in certain individuals following
rapy with arsenicals. Occasional cases developed cirrhosis, and there are at least 3 recorded cases of xanthomatosis as a late complication.[43] Hemochromatosis has also been reported to give rise to a similar picture in rare instances, even to the xanthomatous stage.[24]

Watson and Hoffbauer[46] in 1946 described a clinical picture resembling obstructive jaundice in 9 patients with infectious hepatitis. Several of these developed a biliary cirrhosis, although the majority recovered completely. The transition to biliary cirrhosis from infectious hepatitis was particularly clear in one patient who died at the age of 48 from liver failure after almost continuous jaundice since the age of 15, at which time both she and her sister had an acute episode of jaundice strongly suggestive of ordinary infectious hepatitis.

Recently, evidence has accumulated that methyl testosterone[27, 49] and thorazine[29a] also can produce a clinical picture resembling obstructive jaundice. However, certain differences have been noted. No biliary cirrhosis or xanthomatosis has been observed following these conditions, although the jaundice may be severe and prolonged.[50]

PRIMARY BILIARY CIRRHOSIS OF UNKNOWN ETIOLOGY

The basic etiology of the intrahepatic disturbance in the vast majority of patients with primary biliary cirrhosis is unknown; therefore, this group of patients will be discussed in considerable detail. The evidence available suggests the possibility of a common etiologic factor in the large proportion of these cases. The marked female incidence of primary biliary cirrhosis with xanthomatosis has been evident for a number of years. All of the cases studied by Thannhauser and Magendantz[44] and MacMahon, and Thannhauser[34] were in females. A recent survey of the literature[3] showed only 4 males in a total of 25 cases where adequate exploration of the extrahepatic bile ducts was done and extrahepatic obstruction ruled out. However, two recent reports,[14, 41] covering a total of 19 patients with primary biliary cirrhosis, mainly without xanthomatosis, have not found this female incidence. Ahrens and co-workers[3] collected 17 cases, 9 of which did not have xanthomata, all of which occurred in females. Five additional cases have been collected since this report, also entirely in females. The possibility that females with primary biliary cirrhosis are more prone to develop lipid abnormalities and xanthomata continues to exist, although much of the evidence suggests that the prexanthomatous form is also predominant in females.

No familial or congenital predisposition to this disease has been observed by any of the workers in this field. The national background of the patients also has failed to reveal any specific trend. In the group reported from New York City[3] 7 of the 17 cases occurred in Jewish patients, but this probably reflects the high incidence of this population.

No specific factors have been found to explain the origin of the disease. Careful histories for possible toxic agents, such as arsenicals, hair dyes, methyl testosterone and tolylenediamine, have not furnished clues. Antecedent infection has not been evident in the recently reported cases. Infectious hepatitis has not appeared to be involved, although it is extremely difficult to rule out initial nonicteric episodes. In the majority of patients pruritus was the first symptom,[3] and the disease was insidious in onset without a history of an acute initial episode. A history of allergy has been noted in a considerable number of these patients,[3] which perhaps is of interest in view of the believed sensitivity to arsenicals as causative agents in the postarsenical type of biliary cirrhosis.

Typical Case Report. (Patient E. D., 42-year-old female of Jewish descent, followed at the Rockefeller Hospital and clinic over a period of 6 years.)

The first symptom of her illness was itching of the legs, which began at the age of 34. This gradually became generalized and so severe that the scratch marks required treatment. Approximately 1 year after the onset her physician noted a markedly enlarged liver. There was no jaundice, and the patient never had had pain or fever. She became pregnant at this time, and because of the enlarged liver a therapeutic abortion was carried out. She had had 2 previous children. At this operation the biliary tract was examined and found to be normal. The liver was very large but not nodular. A biopsy was taken, but the report was incomplete. Itching and dark pigmentation of her skin were th main complaints during the following year.

In 1947, at the age of 37 and 3 years afte the onset, the patient was first seen at th Rockefeller Hospital. Physical examinatio showed no jaundice, but there were moderat xanthelasma, marked hyperpigmentation of th skin with areas of depigmentation, particularl on the legs, and enlargement of the liver t approximately 6 fingerbreadths below the costa margin. The patient was well nourished witho evidence of weight loss, and no ascites c edema was found. Laboratory analyses r vealed:

Bilirubin 2.4 mg.%
Bromsulphalein 23% (45 min.)
Albumin 4.2 mg.%
Globulin 3.4 mg.%
Alkaline Phosphatase 60 units (King-Armstrong)
Zinc Turbidity = 29 units

Thymol Turbidity = 5 uni
Prothrombin = 90% of normal
Total Lipid = 1556 mg.
Total Cholesterol = 622 mg.%
Free Cholesterol = 260 mg.%
Phospholipid = 630 mg.

The patient showed little change in her gener condition over the next 3 years as she w followed intermittently as an outpatient. October, 1950, the patient vomited a sma amount of blood. Esophageal varices we readily identifiable. In February, 1951, a seve hemorrhage was controlled by a portaca shunt with an esophageal balloon in place, t operation being performed by Dr. Gardn Childs at Cornell Medical Center. At operati the biliary tract was examined again by retr grade injection and found to be normal. T liver was very large but not obviously nodul Microscopic sections showed marked infilt tion of the portal areas with fibrous tissue such a degree that they were confluent. So inflammatory cells were visible in the por areas, but no dilated bile ducts or bile thro were observed. The liver cells appeared to in good condition, and the lobular patte could still be made out.

The patient gradually improved after stormy period. During the 2½ years since t operation the patient has had no further ble ing, and no ascites has developed. Howev there has been a progressive rise in the ser bilirubin. Table 36 shows the progress changes in certain tests over the 6-year peri The serum albumin level remains fairly g at the present time. Of particular interest is fall in total lipids with the progression of

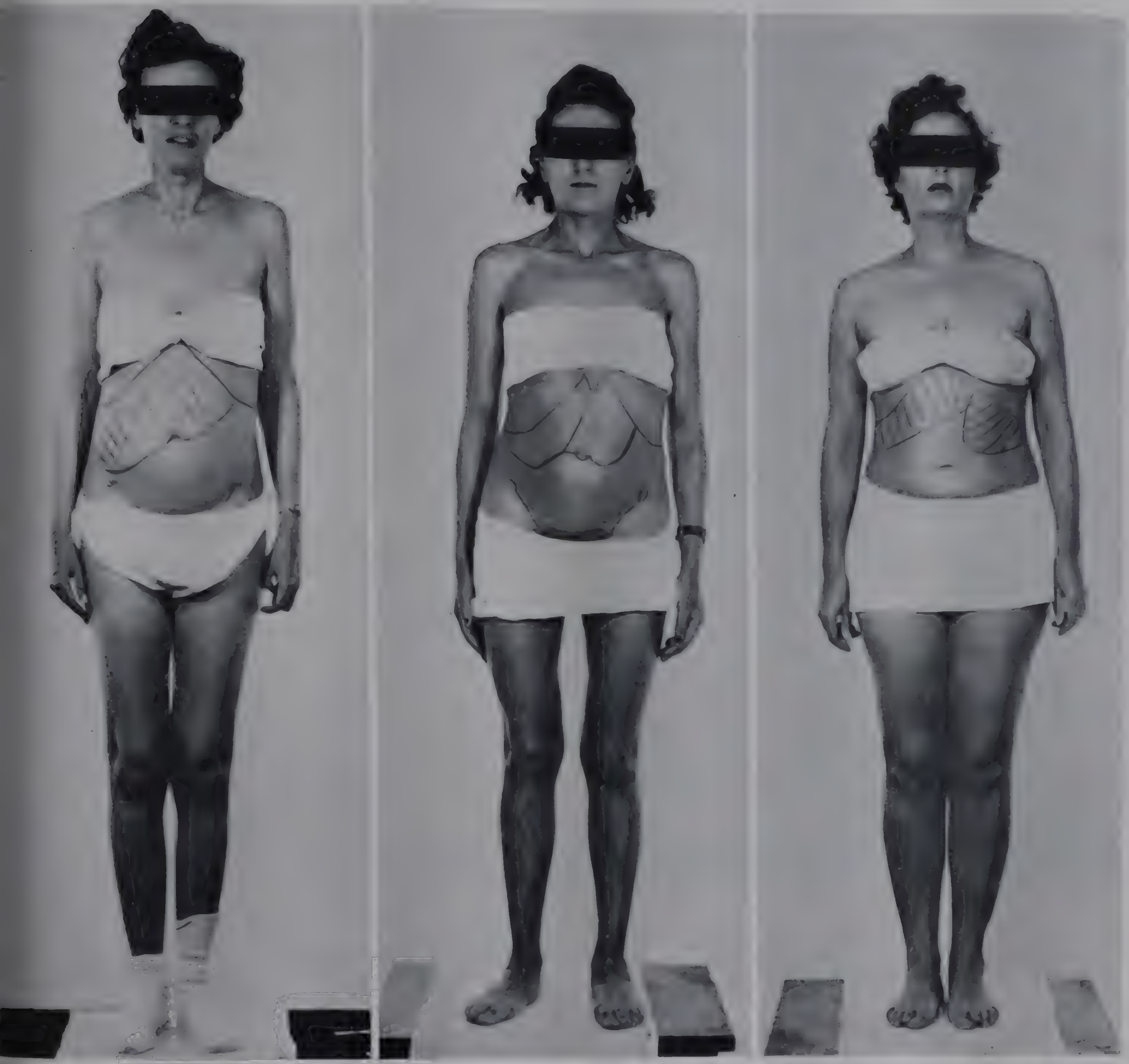

FIG. 132. Three patients with primary biliary cirrhosis. Patient at left had a few flat xanthomata on the face and palms. The patients in the center and at the right showed only xanthelasma. (Ahrens, E. H., Jr., et al.: Medicine 29:299)

TABLE 36

	BILIRUBIN mg. %	SERUM ALBUMIN Gm. %	TOTAL LIPID mg. %	CHOLESTEROL mg. %	PHOSPHOLIPID mg. %
6-24-47	2.4	4.2	1,556	662	640
3-23-48	2.7	4.7	1,340	492	486
11-23-48	2.8	4.1	1,366	435	431
5-17-49	3.2		1,180		
3-14-50	2.6		1,340		
11-21-50	1.6	2.9	850		
2- 8-51	3.0	2.3			
10-23-51	6.6	3.9	560	180	210
7- 8-52	8.9	3.5	680		
1-30-53	9.1	3.0	540		
9-11-53	10.6	3.2	560		

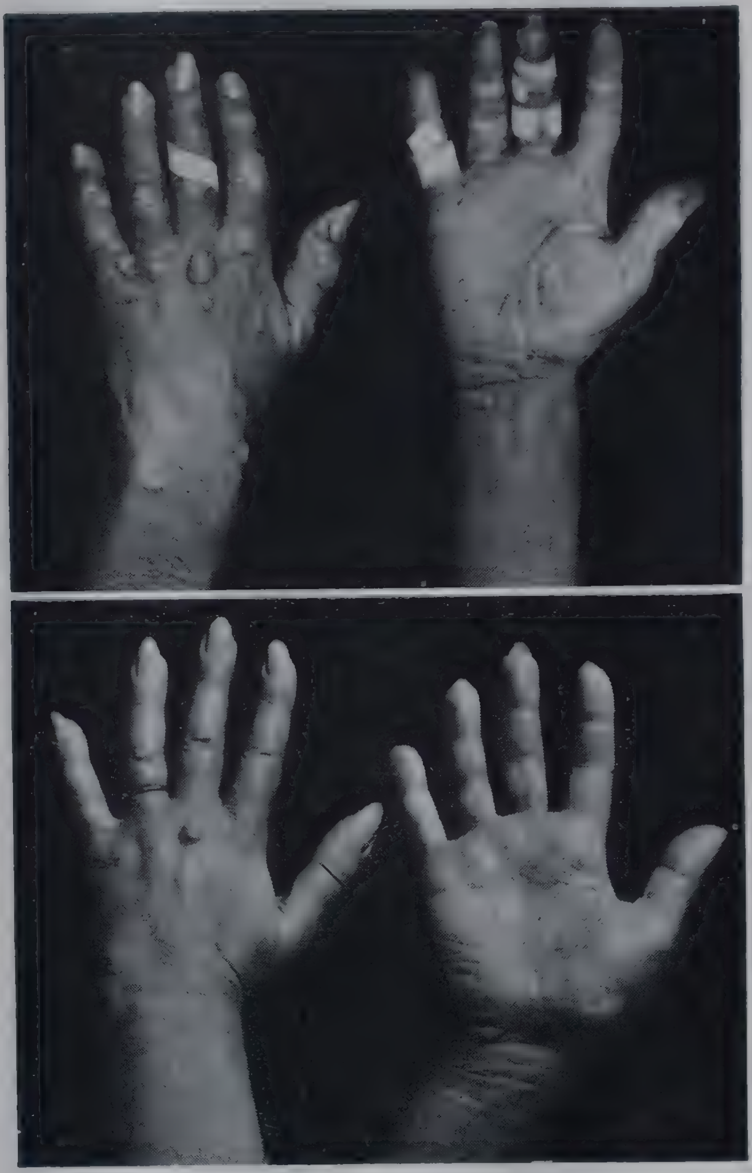

FIG. 133. Disappearance of xanthomata from hands of a patient with primary biliary cirrhosis following a fall in the total lipids of the serum with progression of the disease. The lower photograph was taken 19 months after the upper one. (Ahrens, E. H., Jr., et al.: Medicine 29:299)

disease. The lipid fall was associated with a disappearance of the xanthelasma which had been present for several years. Fig. 132 (*Center*) shows a picture of the patient shortly prior to the portacaval shunt operation.

The history and the course of Mrs. E. D. are typical of most of the patients with primary biliary cirrhosis with an insidious onset with itching as the predominant manifestation, followed by a long period of surprisingly good liver function. This period is characterized by elevation of the serum lipids and the alkaline phosphatase reaction, gradual development of portal obstruction and bleeding from esophageal varices as a late manifestation of the disease, fall in the total lipids c
the serum and a progressive rise in the serur
bilirubin. The elevation in lipids, as in th
majority of other cases, was not sufficient t
produce generalized xanthomata. The onl
atypical feature of this case was the relativel
low bilirubin levels during the first 5 years (
her illness despite other manifestations of re
gurgitation or obstructive jaundice, the sever
itching, the high alkaline phosphatase an
the high serum lipids. However, the dissocia
tion of these findings is observed frequently
Jaundice may be the first symptom and repre
sents the dominant manifestation of the di
ease in the majority of individuals. The symp
toms of pain and fever are conspicuous b
their absence in these patients and serve a
one of the characteristics useful in disti
guishing them from the extrahepatic type.

Steatorrhea represents one of the commo
complications of primary biliary cirrhosi
and a number of the symptoms of the disea
probably stem from this disorder. Soaps ar
increased amounts of free fatty acids we
demonstrated in the feces of almost all of th
patients studied by Ahrens and co-workers
The stools are usually soft, bulky and fr
quent. Relatively flat vitamin A absorpti
curves are found. The marked hyperpigme
tation of the skin frequently observed m
have resulted from vitamin A deficiency b
cause of its association with other types
deficiency of this vitamin. Osteomalacia
often present, particularly in the older p
tients, and probably results from defici
vitamin D and calcium absorption, the latt
through the formation of insoluble calciu
soaps. Pathologic fractures are found in ce
tain of these individuals. Elevated levels
the basal metabolic rate are also characte
istic. These are not due to abnormal thyro
function as indicated by I^{131} uptake studi
They appear to be related to the steatorrh
because of their known occurrence in spr
"Deficiency patterns" of the small bowel a
also characteristic findings by x-ray.

PHYSICAL SIGNS

In general, the patients are found to
fairly robust, active, jaundiced, itching, m
anotic middle-aged women who differ str
ingly from the typical cachetic, pale, p

bellied males with portal cirrhosis. Jaundice, skin changes, including hyperpigmentation and xanthomata, and markedly enlarged liver and spleen represent the most characteristic physical signs. The skin changes are decidedly variable and differ in each patient. The skin is usually thickened, coarse and somewhat dry, with a papular dermatosis over the arms and the legs. The scratching due to the itching confuses the picture, but vesicles appear which develop into hard papular nodules. Depigmented areas of the skin occur at the sites of old lesions. Hyperpigmentation in surrounding areas has been mentioned already as very characteristic. Addison's disease and hemochromatosis have been diagnostic considerations because of this physical sign.

Xanthomata appear in certain of these patients, depending on the lipid alteration. Yellowish infiltrations in the skin usually are observed first in the eyelids, particularly at the inner canthi. Two major types of xanthomata may then follow. The flat type similar to those around the eyes may involve the palms, the neck, the chest or the back. The tuberous variety usually are found over the knuckles, the wrists, the elbows, the knees, the ankles and Achilles tendons. The distinction between these 2 types is not always clear cut, and when either type is confluent they are difficult to classify. A definite tendency for xanthomata to develop over pressure points and the site of old injuries has been recognized for a long time. These skin manifestations usually are not disabling except when they develop largely over the hands and the ankles in regions where they are susceptible to trauma (Fig. 133).

All observers have stressed the marked enlargement of the liver found in these patients which is similar in degree to that found in patients with chronic extrahepatic biliary obstruction. Even in the late stages of the disease when complications of liver failure set in, particularly ascites and esophageal hemorrhages, the liver enlargement persists. Moderate splenomegaly appears to occur to a variable extent in the majority of patients. Spider angiomata appear relatively infrequently as contrasted with other types of cirrhosis. Generalized lymphadenopathy was observed in a large percentage of the patients studied by Ahrens and co-workers.[3] This is of interest in view of the frequency with which enlarged nodes are noted along the portal vein and the common bile duct at laparotomy or autopsy.

With progression of the disease, esophageal varices with resulting hemorrhages are common, considerably more so than ascites. Patients often bleed who are in relatively good general condition. Portacaval shunts have been of value in a number of these patients.

LABORATORY FINDINGS

Since the manifestations of partial biliary obstruction are the major clinical features of primary biliary cirrhosis, the laboratory tests also primarily reflect this aspect of the disease. Elevations of serum bilirubin, serum alkaline phosphatase activity, total serum lipids, urine bile and urobilinogen and fecal fatty acids with depression of fecal urobilinogen are characteristic findings. The manifestations are usually not those of complete biliary obstruction, although this is found in some patients terminally. In the latter patients clay-colored stools and absent or extremely low fecal and urine urobilinogen are observed.

Very high levels of alkaline phosphatase have been found almost universally in these patients. Values as high as 106 and 116 King-Armstrong units have been reported.[3] Certain patients show a fall to normal levels during certain stages of the disease, particularly with progression of the signs of hepatic insufficiency. Here there is a dissociation of the phosphatase and the bilirubin levels. However, the majority of patients continue to show very high values throughout their course.

The serum lipids are very abnormal in the majority of patients. Since this aspect of the disease does not differ in any way from that observed in secondary biliary cirrhosis, it will be considered as a separate subject in a later portion of this paper.

Routine liver function tests show small abnormalities, at least in comparison with those observed in other types of cirrhosis, during the first years of the disease. Even terminally, in some patients, the capacity of the liver to perform certain functions remains surprisingly good. This is particularly demonstrated by the serum albumin levels. Values below 3 Gm. per cent are unusual except during the periods following severe hemorrhages. Values above 4 Gm. per cent are often seen for years during the early stages despite the fact that the bilirubin may be persistently elevated. Abnormalities in the globulins of the serum are somewhat more marked. The zinc turbidity is definitely elevated in the vast majority of patients in contrast with the low levels found in simple obstructive jaundice. Electrophoretic patterns[3, 41] have confirm the elevated gamma globulin levels and al have shown very high β globulin peak These have been found to be due to lipopr teins formed in association with the hi phospholipid and free cholesterol of the sera.

Studies of other proteins that are depress in severe liver disease have revealed su prisingly good levels in these patients. Pr thrombin values in the author's experien were usually normal when adequate vitam K was supplied. A good response to this vit

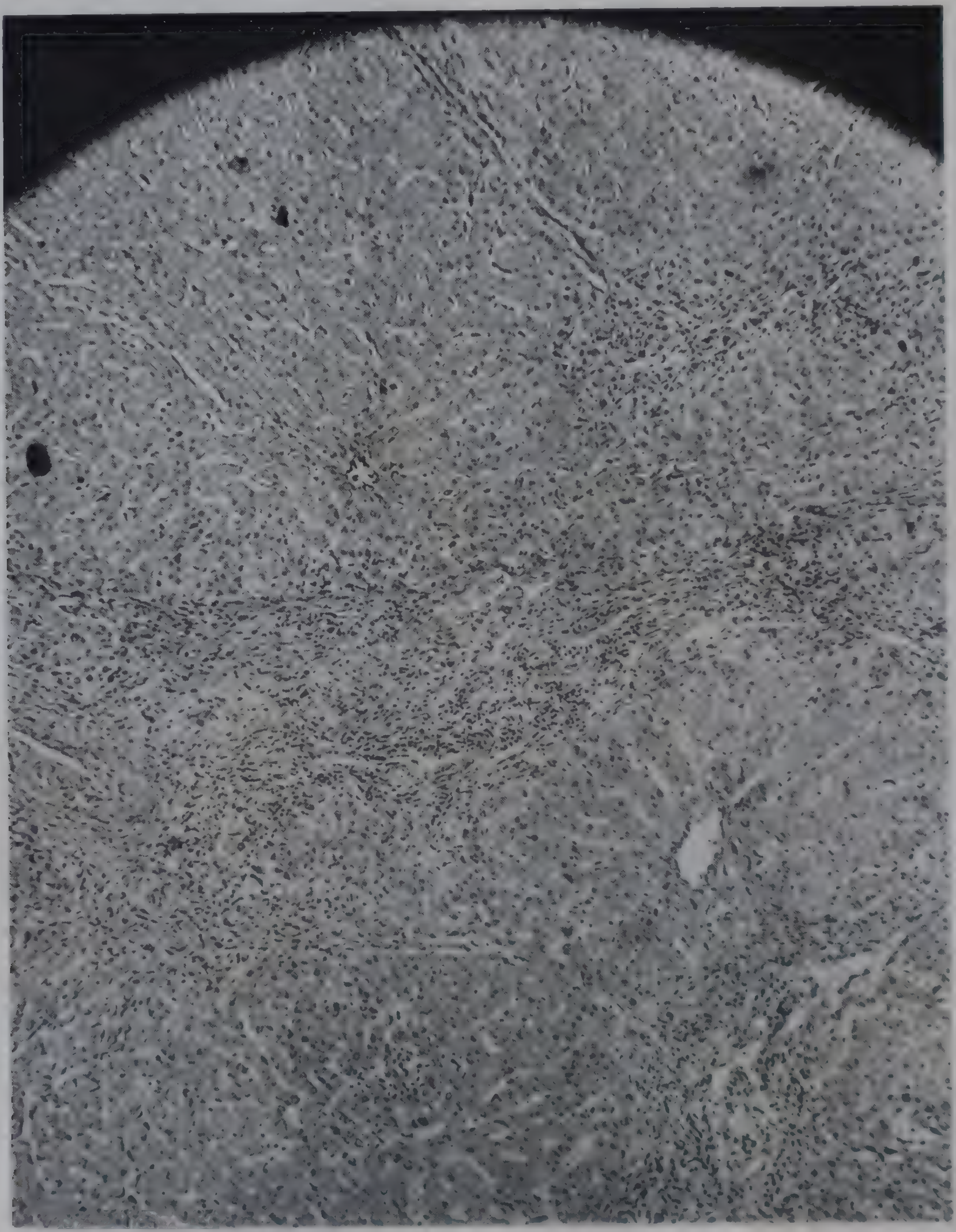

FIG. 134. Section of liver taken at laparotomy from a patient with primary biliary cirrhosis. The infiltration of inflammatory cells and fibrous tissue in the portal areas, along with a relatively intact lobular pattern, can be seen.

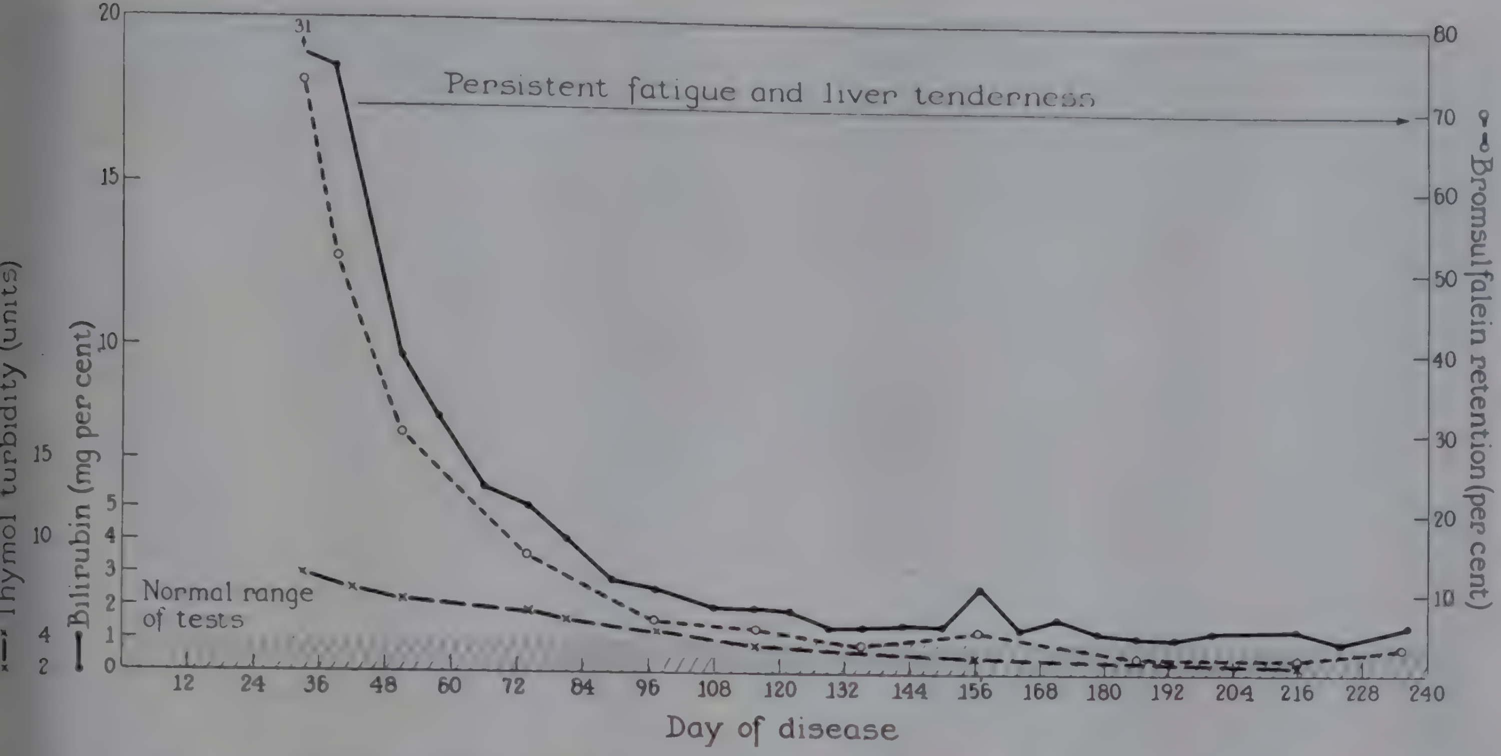

FIG. 135. Extreme elevation of the bilirubin level of a patient with infectious hepatitis out of proportion to other liver function tests, suggesting the obstructive type of jaundice; relatively slow recovery. (Kunkel, H. G., et al.: Ann. Int. Med. 27:204)

min in untreated individuals was good evidence of the preservation of hepatic cellular function in these patients, particularly in contrast with patients with classical Laennec's cirrhosis. Serum esterase levels are usually lower than normal, but they are not depressed to the degree observed in other types of cirrhosis.

The results of the cephalin flocculation and thymol turbidity tests are more variable. Four plus reactions for the former test are observed often but usually in the later stages of the disease. The thymol turbidity test, as in other types of cirrhosis, shows great variation in different patients with little relation etween the degree of abnormality and the xtent of liver damage. Some correlation xists with the degree of hyperlipemia, but he relationship is less direct than is observed n the hyperlipemia of nephrosis. The bromulphalein test is of little value because of he hyperbilirubinemia observed in most of hese patients. High values are found almost niversally.

PATHOLOGY

The pathology of primary biliary cirrhosis vas elucidated considerably through the work f MacMahon and Thannhauser,[34] although these workers limited their observations to xanthomatous cases. A review of the sections obtained from the nonxanthomatous patients described by Ahrens and co-workers[3] was undertaken by MacMahon, and he considered the changes to be essentially similar in nature in the two groups. In the early cases the primary abnormality is a nonspecific inflammatory reaction in the portal areas at the periphery of the lobules, concentrated about the smallest interlobular bile ducts or cholangioles and the junction ducts. Bile plugs are observed in the canaliculi in some cases. The larger size ducts are not dilated and often are difficult to find. As the disease progresses, inflammatory granulation tissue and fibrous tissue are observed spreading out from the peripheral zones of the lobules to form a connecting network. Even at this stage the lobular pattern is preserved, and the liver cells remain in good condition (Fig. 134). With further progression of the disease at the time the majority of these patients come to autopsy, distortion of the lobular pattern is observed, and in some cases many of the liver cells have been destroyed.

Considerable similarity in the microscopic sections from different patients with primary biliary cirrhosis usually is found. The lesion about the smallest interlobular bile ducts is

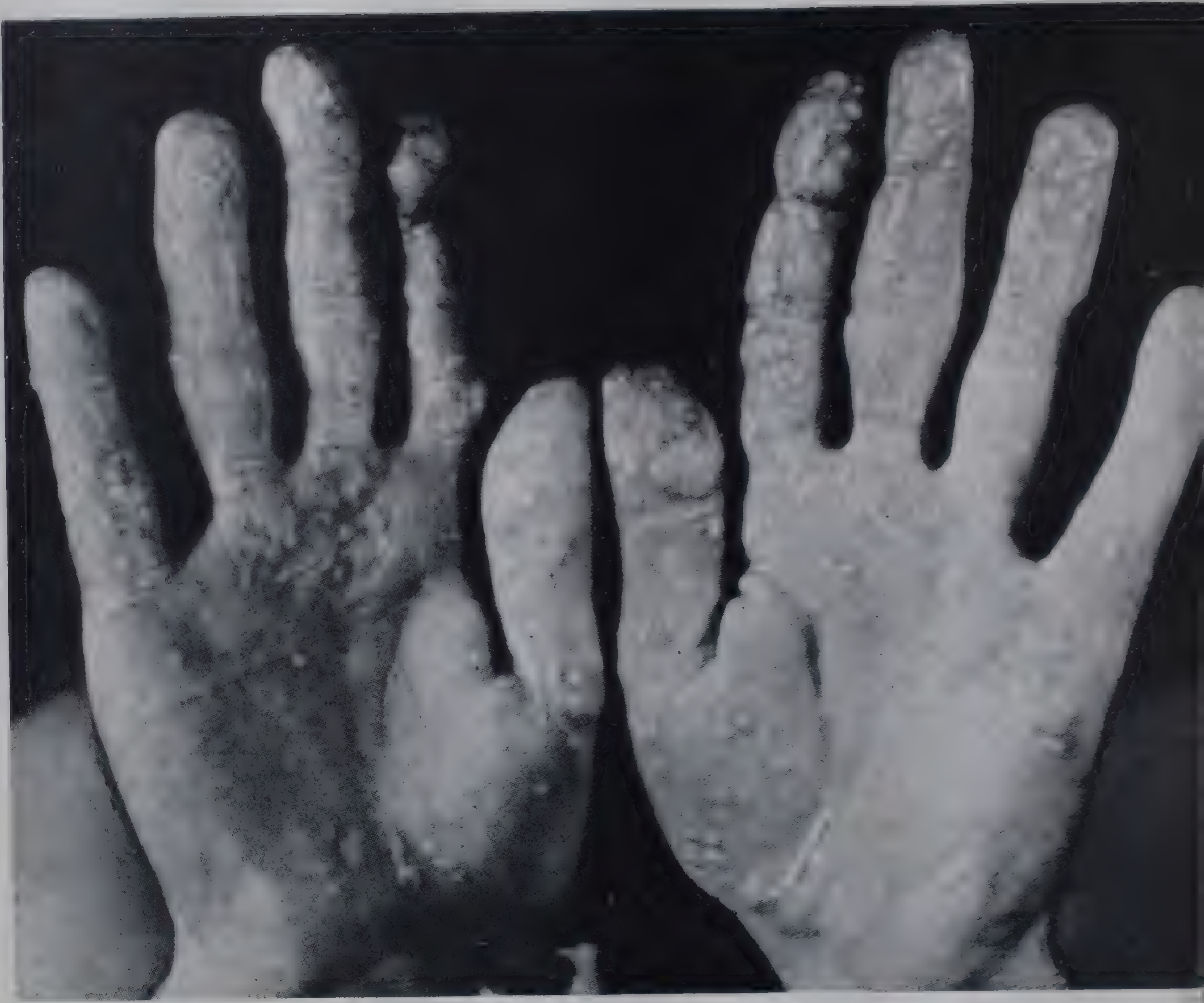

Fig. 136. Xanthomata appearing in a case of postarsenical biliary cirrhosis. (Chanutin, A., and Ludewig, S.: J. Lab. & Clin. Med. 22:904)

characteristic of this disease, although sometimes it is difficult to recognize in the late stages. However, the lesion is not specific for these cases of primary biliary cirrhosis of unknown etiology. Similar changes have been termed cholangiolitic cirrhosis of the liver following infectious hepatitis. In addition, a few cases of postarsphenamine jaundice have shown a similar progression in terms of histologic changes.[20, 43]

PRIMARY BILIARY CIRRHOSIS OF KNOWN ETIOLOGY

Considerable evidence has accumulated that infectious hepatitis can give rise to a type of primary biliary cirrhosis in certain rare instances.[42, 46] All clinicians who have observed patients with infectious hepatitis
have seen certain cases where the class
manifestations of hepatocellular damage
scarcely evident, while the signs, the sy
toms and the laboratory findings of obst
tive jaundice predominate. Figure 135 il
trates such a case in a young Navy man w
the jaundice was out of all proportion to
seen in other cases and the liver-func
tests, usually abnormal in these patie
showed surprisingly good values. The thy
turbidity test showed relatively low levels
was in the normal range during the m
part of the course while jaundice and sy
toms of fatigue persisted. The cephalin
culation test was 2+ on admission, b
other determinations thereafter were ei
negative or 1+. The total cholesterol
elevated to 420 mg. per cent with a F
Total ratio of 0.35. The phospholipid

lso very high at 510 mg. per cent. Unforunately, total lipids and alkaline phosphatase leterminations were not done. However, the esults obtained suggested an obstructive type of jaundice. This patient had persistent sympoms for 2 years but showed eventual comolete recovery with the exception that the ilirubin level was elevated at 1.4 mg. per ent on one occasion 4 years after the initial ttack. No biopsy was obtained. Other workrs have observed inflammatory changes round the smaller bile ducts in the portal reas as the only pathologic changes in cerain patients with infectious hepatitis. Such a esion might be considered to progress and ead to gradual fibrosis as has been described. No definite cases of this type have been oberved by the author, but the experience with atients such as the one illustrated makes it eem likely that such cases do develop.

In 1940 Hanger and Gutman[20] reported 12 cases of postarsphenamine jaundice where he clinical manifestations and the laboratory ests suggested an obstructive type of jaunlice. Several of their patients came to surgery, and the extrahepatic bile ducts were hown to be patent. Biopsies of the liver howed an inflammatory reaction around the mall interlobular bile ducts in the portal reas. Bile plugs in the canaliculi within the obules were very prominent. Slight fibrosis round the inflammatory regions was noted, out all of these patients recovered. High evels of bilirubin, alkaline phosphatase and holesterol with relatively normal cephalin locculation reactions were emphasized. A umber of subsequent reports[9, 43] have conirmed these observations. In addition, xanhomatosis and a real biliary cirrhosis have een found to develop in certain of these ases. Figure 136 shows the xanthomatous esions in one particularly well documented ase.[9] Microscopic sections showed interobular fibrous tissue extending from the poral spaces. The picture closely resembled that lescribed above for primary biliary cirrhosis f unknown etiology.

In these cases the evidence is strong that he lesion results from a specific sensitivity o arsenic rather than to a direct effect of this netal on the liver cells. It suggests the posibility that in the cases where the etiology is unknown a sensitivity to some as yet unidentified substance may be at fault. In the reported cases of xanthomatosis associated with postarsphenamine jaundice a slight male incidence has been found. This differs strikingly from the marked female incidence of biliary xanthomatosis of unknown etiology and demonstrates that males under the proper inciting agents also can develop extreme lipid changes and xanthomata.

A number of cases of hemochromatosis have been reported[23, 34] where secondary elevation of the serum lipids and xanthomata have developed. The autopsy findings have not been described in sufficient detail to determine whether or not these cases can be classified as biliary cirrhosis secondary to the hemosiderosis. However, as a result of the clinical findings, it seems probable that the small bile channels in the liver were involved somewhat selectively in these cases, producing the obstructive or regurgitation manifestations. The 3 cases that have been well studied were all in males, again indicating that the high lipids and the xanthomata need not develop primarily in females as in primary biliary cirrhosis of unknown etiology.

Recently, another causative agent producing an obstructivelike jaundice in humans has been demonstrated to be methyl testosterone. Kinsell[27] first noted jaundice in patients receiving this medication, and the clinical and pathologic picture resulting from this complication was distinctly classified by Werner and Hanger.[49] The latter authors recorded 7 cases where methyl testosterone was clearly implicated in the production of jaundice. Relatively low cholesterol and alkaline phosphatase levels were noted, and in this respect the clinical findings differed from those usually encountered in obstructive jaundice. Biopsies of the liver showed bile plugs in the intralobular canaliculi as the sole pathologic feature. Recently, Wood[50] has reported a case of severe and prolonged jaundice following methyl testosterone, but a real biliary cirrhosis has not been observed. In addition to those sporadic instances of jaundice in normal individuals, methyl testosterone in the author's experience frequently produces an elevation of bilirubin in patients with biliary cirrhosis. Methyl testosterone also has other effects in these patients. Frequently, the severe itching is relieved, and certain of the patients show a fall in serum lipids while on this medication.[3, 30]

These effects of methyl testosterone, along with the female sex incidence of primary biliary cirrhosis of unknown etiology, raises the question of whether certain of the steroid hormones may be implicated as causative agents in this disease. A beneficial effect of pregnancy reported in one case[41] and unusual effects of estrogens[3] also are suggestive. However, no direct evidence of such an etiologic relationship has been obtained.

Very recently, a considerable number of cases of obstructive jaundice have developed after Thorazine (chlorpromazine) administration. Of particular interest is the development of eosinophilia in many of these patients.[29a] Sulfonamides, thiouracil and butazolidine are 3 other drugs that also have been implicated in producing this picture in rare instances.

SECONDARY BILIARY CIRRHOSIS

Two major types of biliary cirrhosis secondary to a chronic obstructive lesion in the extrahepatic biliary system are encountered. The first type resulting from congenital atresia of the bile ducts is limited to children; the second type, due to traumatic or pathologic processes involving the bile ducts, occurs primarily in adults. The first type is of particular interest because the congenital atresia of the bile ducts may be the sole abnormality, and the progression of the obstructive jaundice to biliary cirrhosis may be seen readily. This is not as uncommon an abnormality as is sometimes supposed; at least 300 cases have been recorded in the literature.[13, 36] Unless early surgical therapy has relieved the obstruction, some degree of biliary cirrhosis usually is apparent when these children come to autopsy. Connective tissue proliferation in the portal areas has been noted as early as 6 weeks after birth in certain cases,[36] indicating the rapidity with which cirrhosis may develop in cases of complete atresia of the extrahepatic ducts. Five and a half months of age has been estimated as the time at which irreversible biliary cirrhosis sets in and patients no longer respond
to surgical removal of the obstruction. E
phageal varices have been observed as e
as 2 months of age,[36] and ascites at 4 mon
In addition to cirrhosis, bile duct prolif
tion and dilatation of the larger ducts in
liver are prominent pathologic findings. C
siderable literature has accumulated rega
ing the presumed role of infection in
biliary tract along with obstruction in
ducing secondary biliary cirrhosis in adu
However, the rapidity of the developmen
cirrhosis in the children with complete atr
of the extrahepatic ducts, where no infec
is apparent, suggests that this concept d
not necessarily hold.

The other manifestations of biliary cirr
sis seen in adults, particularly the mar
serum lipid alterations and xanthomata,
ally are not observed in the children
extrahepatic atresia, primarily because
obstruction is usually complete and they
not live a sufficient length of time with
surgical intervention to develop these c
plications. In another group of patients
congenital absence of the intrahepatic
ducts the lipid complications are seen,
generalized xanthomata may develop.
cently, these patients have been studie
considerable detail by Ahrens, Harris
MacMahon.[4] Possibly they should be cl
fied with primary biliary cirrhosis, bec
the intrahepatic lesion predominates. T
patients, although they often show e
hepatic biliary atresia along with the abs
of intrahepatic bile channels, do not ap
to develop severe cirrhosis as rapidly
may live to be several years old. Genera
skin xanthomata, along with severe ab
malities in the phospholipid and free
lesterol fraction of the serum, were n
in each of the 4 patients described by Ah
and co-workers.[4] Three of the patients e
tually died, and one remains alive at the
of 7 years. A biliary cirrhosis was note
autopsy in each case, but no bile ducts c
be found. Bile plugs in the intralobular c
liculi were prominent. Figure 137 illust
one of these patients, showing particu
the extensive xanthomata over various
tions of the body. In the patient who rem
alive the serum lipids have showed rec
a considerable fall to close to normal l
and at the same time the xanthomata

isappeared entirely. A similar relationship etween the duration and the degree of serum pid abnormality and xanthomatosis was oberved in these patients as in the individuals ith primary biliary cirrhosis.

The other major type of secondary biliary irrhosis is that due to prolonged biliary obruction in the extrahepatic ducts resulting om some pathologic process occluding the ucts. The literature on this type of biliary rrhosis remains considerably more confused nd uncertain than in the case of congenital resia. This is chiefly due to the multiplicity f causative agents that may initiate the obruction and to the fact that the disease rocess producing the obstruction may prouce generalized effects of other sorts that onfuse the over-all picture. In addition, secndary infection in the bile duct system is equently present, and the role this plays the development of cirrhosis is obscure.

The types of obstructive lesions that have ad to biliary cirrhosis are decidedly variae. In general, benign lesions, particularly e type leading to prolonged intermittent ostruction, are more prone to lead to a rrhosis. Probably the most common type sults from surgical injury of the extraepatic ducts, particularly following gallblader removal. Common-duct stones usually e considered as the next most frequent use. Other causes are much less common. ccasionally, carcinoma of the ampulla of ater, hydatid cysts of the common duct and rcinoma of the gallbladder are the causave agents. The obstruction resulting from alignant lesions, such as carcinoma of the ad of the pancreas, are usually of insuffient duration to bring about a true cirrhosis.

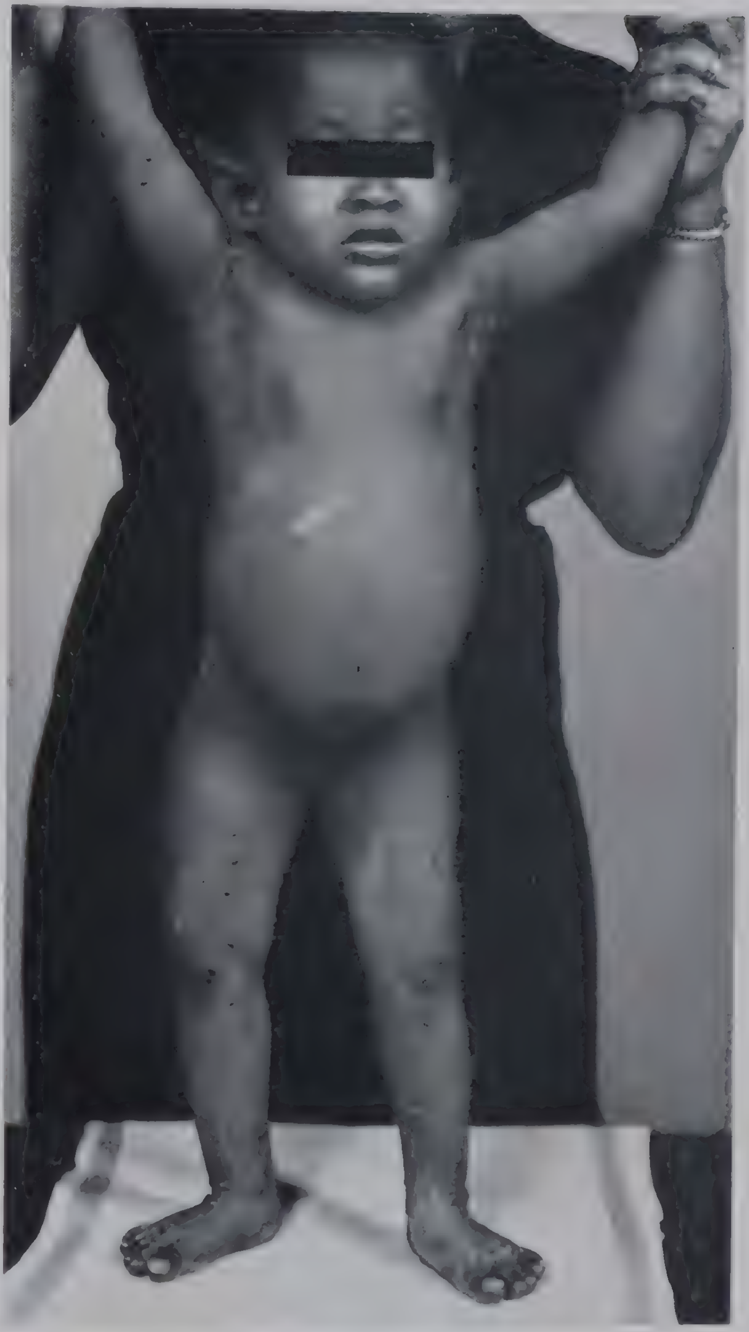

FIG. 137. Xanthomata in a 3-year-old patient with very high serum lipids associated with congenital absence of the intrahepatic bile ducts. (Ahrens, E. H., Jr., et al.: Medicine 29:299)

Various figures for the over-all incidence biliary cirrhosis following any type of exahepatic biliary obstruction have been ven. The series of Gibson and Robertson,[19] hich is probably the most nearly complete any that are available, lists an incidence 8.6 per cent of cases of cirrhosis among group of 244 cases showing extrahepatic liary obstruction at autopsy. Most other ries are reported as the incidence of obuctive lesions among cases of cirrhosis und at autopsy. Mallory[31] reported that 29 per cent of a group of 487 cases of cirosis were obstructive in origin. However, relatively few of these cases develop a sufficiently severe cirrhosis to result in esophageal hemorrhages and ascites, although a cirrhosis is apparent in pathologic sections. Formerly, these patients were seen more frequently; at present the obstructive lesion usually is removed, relieving the obstruction and preventing the late manifestations of cirrhosis. Even in cases of inoperable carcinoma, sometimes the obstruction is removed as a palliative measure. In other cases death ensues before a real cirrhosis develops. In the author's experience the primary biliary cirrhosis of unknown etiology has been encountered more frequently in a liver disease clinic than the secondary cirrhosis. During a period when 22 cases of the primary type were observed, only 4 cases of the secondary type were seen. This probably represents a partial selection of cases because of the lack of close connection with surgical groups where the latter cases usually are seen. In respect to the cases developing xanthomatosis, Ahrens and co-workers collected from the literature 24 cases of the extrahepatic type as compared with 25 cases of primary biliary cirrhosis. Only 3 of the 24 cases of xanthomatosis following extrahepatic obstruction were found in cases of carcinoma, and none represented carcinoma of the pancreas. The development of xanthomatosis also requires the presence of the obstructive lesion for a considerable period of time. The shortest period noted in the literature is 9 months, most cases having partial or intermittent complete obstruction from 3 to 10 years.

The type of adult patient most frequently seen at the present time with secondary biliary cirrhosis is one who has had numerous operations on the extrahepatic biliary system with temporary and partial relief of numerous obstructive episodes. However, the cumulative effect of the numerous episodes has resulted in a moderate cirrhosis. A female incidence has been noted by several groups. Gibson and Robertson[19] found 7 males and 14 females in their series. The cases of xanthomatosis with proved extrahepatic obstruction collected from the literature by Ahrens and co-workers[3] showed 7 males and 17 females.

TYPICAL CASE REPORT. (Patient M. G., 60-year-old female.) The illness began in 1943 with bouts of severe right upper quadrant pain associated with nausea and apparently related to the ingestion of fatty foods. The pain persisted intermittently for the next few years. In 1947 a stone was noted in her gallbladder by roentgenogram, and a cholecystectomy was performed. Five months after operation jaundice and generalized pruritis developed. She was subjected to a second laparotomy, and the common duct was palpated and explored with an aspirating needle. No obstruction was found. During the next 1½ years she was observed in various hospitals, complaining continually of
severe jaundice and itching. She was firs
served at The Rockefeller Hospital in No
ber, 1948. Physical examination show
jaundiced woman in good nutritional state
liver was palpable 8 fingerbreadths belov
costal margin. There was no ascites or ec
Liver function studies showed a bilirub
10.9 mg. per cent, cholesterol 645 mg. per
alkaline phosphatase 65 Bodansky units,
min 3.3 mg. per cent, globulin 5.7 mg
cent, zinc turbidity 35 units and thymo
bidity 5 units. Because of the continue
structive manifestations another explor
laparotomy was carried out. This time a
cut stricture of the common duct was fou
a mass of adhesions. An end-to-side a
mosis of the jejunum and a stub of th
hepatic duct was performed, along wi
enterostomy. Following operation her
became dark, and the bilirubin fell to
ranging from 0.9 to 2.7 mg. per cent
patient was considerably better, and liver
tion improved. However, she continued tc
bromsulphalein retention of 25 to 30 per

The patient remained well until Septe
1952, when she developed an acute att
epigastric pain, fever and chills, and th
rubin level rose to 10.6 mg. per cent. A
laparotomy was carried out, entailing a
procedure on the choledocho-enterostom
opsy of the liver showed moderate cir
with increased fibrous tissue in the portal
numerous inflammatory cells and redupli
of the bile ducts. Again, improvement fol
Several further obstructive episodes
1953 may make further surgery likely.

The history and the course of Mrs.
is typical in that the biliary cirrhosis
oped following a postcholecystectom
duct stricture which caused obstructive
festations continually for over 2 year
spite this long period, marked improv
in liver function occurred following s
relief of the obstruction, although a mc
cirrhosis remains.

Perhaps the outstanding sympton
helps to distinguish the extrahepatic
the intrahepatic types is pain. Freque
is found in the former group and ra
ever, in the primary type. None of th
of primary biliary cirrhosis report
Ahrens and co-workers[3] had abdomin
at any time during their illness.
function tests in secondary biliary ci
show relatively good liver function, pr

longer than in the primary group. Serum
min levels and prothrombin times after
min K are usually close to normal, despite
iderable fibrous-tissue invasion. In gen-
the pattern of liver function tests closely
mbles that described for primary biliary
osis. This also applies to the serum lipid
ations. High levels of cholesterol and
spholipid are characteristic, but normal
ls are encountered frequently. As in the
ary type, a certain percentage of patients
vs a lipid elevation sufficient in degree
and duration to result in xanthomatosis. The skin lesions are similar in the 2 types.

In pathologic sections the distinction between the primary and the secondary types is often clear, due to the great reduplication of bile ducts in the portal spaces and dilatation of the larger ducts usually observed in secondary biliary cirrhosis (Fig. 138). Relatively normal lobules, along with inflammatory cells around the large and the small ducts and fibrous-tissue infiltration in the portal areas, are observed also in the sec-

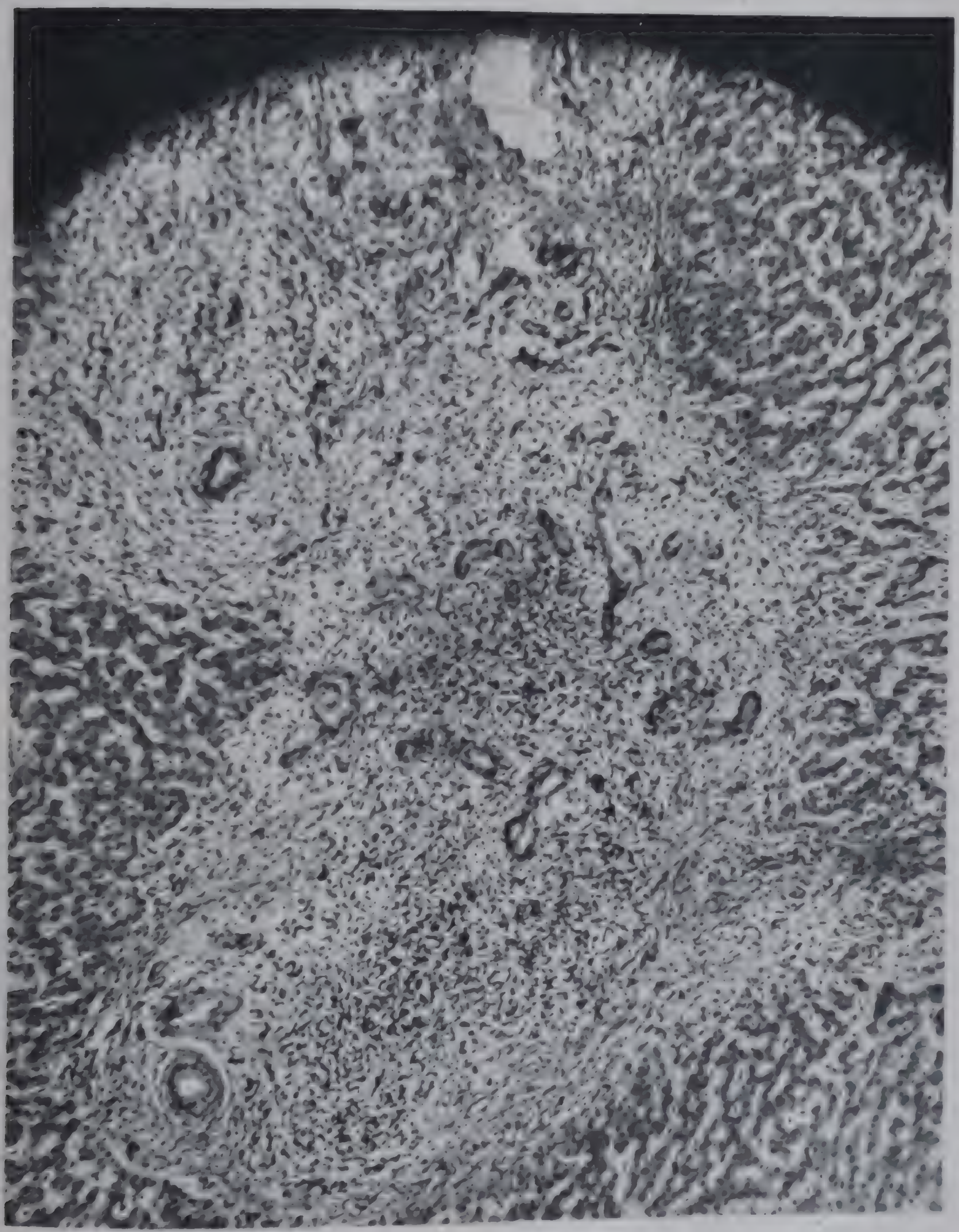

FIG. 138. Section of liver obtained at laparotomy in a patient with long-standing intermittent extrahepatic obstruction. Inflammatory granulation tissue and fibrous tissue around the reduplicated bile ducts can be seen.

ondary cases but aid little in distinguishing them from the primary group.

LIPID ALTERATIONS AND XANTHOMATOSIS

Because of the specific nature of the lipid disturbance found in many cases of primary and secondary biliary cirrhosis, as well as in uncomplicated biliary obstruction, this subject will be considered in some detail, particularly in relation to the development of xanthomatosis in certain of these patients. The first realization of an association between elevated serum lipids and xanthomata appeared in 1878 in an article by Chambard.[8] He reported a case of biliary cirrhosis and xanthomata due to a hydatid cyst compressing the common bile duct. The total blood fat content was reported in this case by Quinquand as 6 times the normal. He also showed that the affected areas of skin had fat levels from 3 to 4 times that in the unaffected areas. A considerable period of time passed before more detailed lipid studies were carried out. In 1927 Dyke[15] described a case of obstructive jaundice resulting from a chronic inflammation in the head of the pancreas. Xanthomata developed, and a cholesterol analysis on the serum showed a value of 1,250 mg. per cent. Of the total cholesterol only 220 mg. per cent was in the ester form. In 1932 Bürger and Grütz[5] described a case of obstructive jaundice with xanthomatosis where the blood lipids were: total cho terol, 2,575; free cholesterol, 1,444; c lesterol esters, 1,131; lecithin, 3,045; total lipids, 5,872. They emphasized the that lecithin represented 52 per cent of total lipid. A second case in a young also showed very high lecithin levels. S sequently Thannhauser and Magendan and Montgomery[35] further characterized lipid abnormality in biliary xanthomat The latter stressed the marked increas free cholesterol as well as lecithin in blood and tissue lipids.

The first mention of the presence of c serum, despite very high cholesterol val probably appeared in a paper by Weid and Boston in 1937.[48] They noted the c serum in a case of biliary cirrhosis follo obstruction of the common duct by a pc despite a cholesterol level of 1,020 mg. cent. Subsequently, MacMahon and Tha hauser[34] and Ahrens and co-workers[3] phasized the remarkable clarity of extre high lipid sera in patients with both prir and secondary biliary cirrhosis. The la authors noted only 1 case of the 18 studied at frequent intervals that showed nite opalescence of fasting serum. This se contained a higher neutral fat level than of the others. In most cases the neutra was close to normal. This is in marked trast with most other hyperlipemic s where the neutral fat fraction is usually most abnormal.[3] Figure 139 shows the se

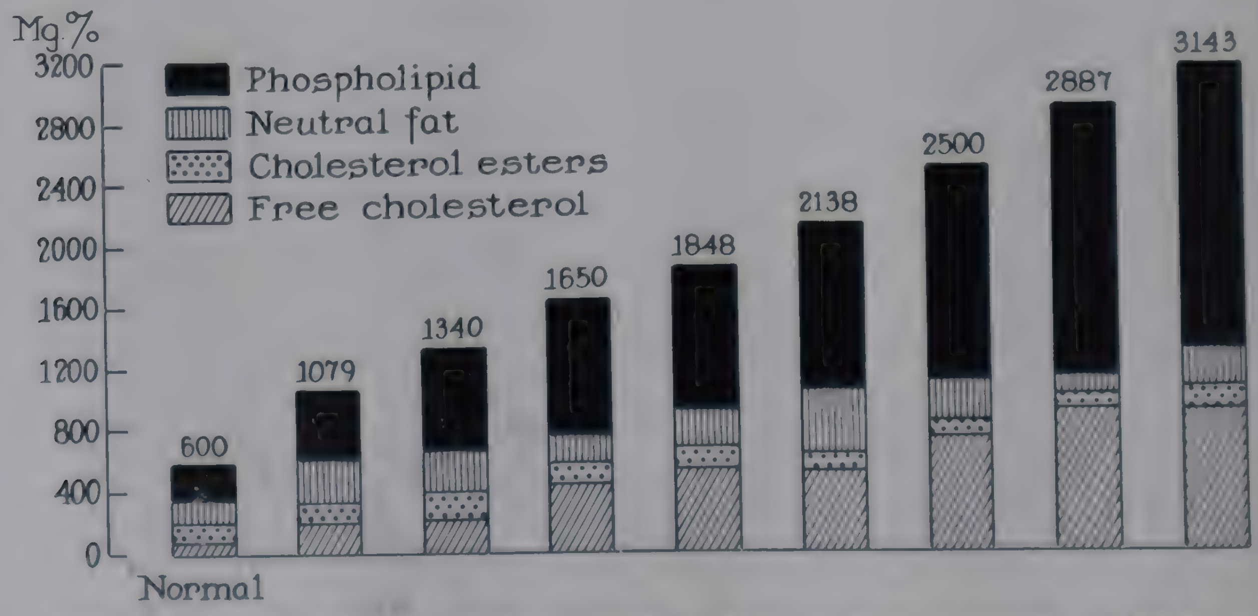

FIG. 139. Lipid pattern in the serum of 8 patients with primary biliary cirrhosis. The unusual elevation of the phospholipid and free cholesterol fractions is apparent. (Ahrens, E. H., Jr., and Kunkel, H. G.: J. Clin. Invest. 28:1565)

TABLE 37. COMPARISON OF AVERAGE CHOLESTEROL AND PHOSPHOLIPID LEVELS IN A GROUP OF NORMAL INDIVIDUALS AND 18 PATIENTS DURING THE ACUTE STAGE OF INFECTIOUS HEPATITIS
(Eder and associates)

	NORMALS	INFECTIOUS HEPATITIS
holesterol	190	151
hospholipid	227	318
ree/Total Chol.	0.29	0.80
hol./P lipid	0.86	0.49

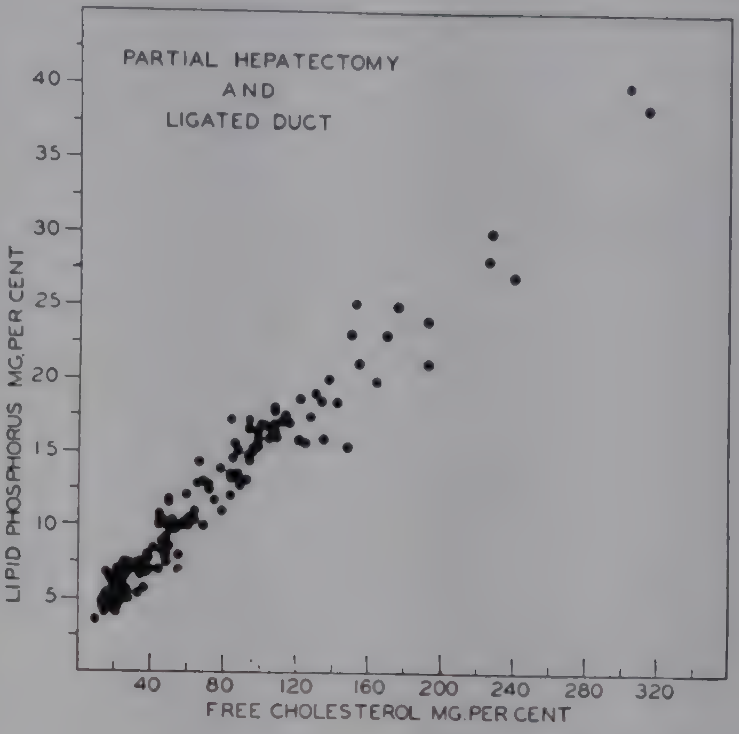

FIG. 140. Association of free cholesterol and phospholipid in the serum of rats subjected to bile duct ligation. (Chanutin, A., and Ludewig, S.: J. Biol. Chem. 115:5)

oid patterns from 8 different patients with imary biliary cirrhosis. The preponderant evation in the phospholipid and free cho- sterol fractions is apparent. This typical oid pattern is found also in patients with trahepatic biliary obstruction as well as in any patients with acute infectious hepati- . Table 37 shows data recently compiled ' Eder and associates[16] in patients with patitis. The high phospholipid and free olesterol fractions give these sera a lipid ttern similar to those obtained from pa- nts with biliary cirrhosis. Certain patients monstrate this alteration more strikingly an others, as may be seen from the studies Man and Peters.[32] Chanutin and Lude- g,[10] in 1936, emphasized the free choles- ol phospholipid relationship in rats sub- cted to common bile duct ligation. Figure 0 shows the close correlation obtained by ese workers. Although some instances of rtial hepatectomy are included in this art, the high values for free cholesterol d phospholipid are all from the animals th biliary obstruction, and these account ' the correlation.

Recently, considerable interest has cen- ed on the state of the lipids in these sera, d various technics for the study of the oproteins involved have been carried out. ne electrophoresis in various supporting dia[28] has indicated that the great predomi- nce of the cholesterol and phospholipid ctions are bound to proteins and migrate h an electrophoretic mobility similar to the rmal β lipoprotein. Lipoproteins with mo- ities similar to the normal α lipoproteins reduced or completely absent in these sera. By chemical fractionation employing methods similar to those developed by Cohn and his co-workers, Eder and associates[16] have isolated a lipoprotein fraction consisting of phospholipid and free cholesterol without significant amount of ester cholesterol. Table 38 presents some of their results in sera from patients with biliary cirrhosis. These workers have noted this unusual lipoprotein fraction only in sera of patients with biliary obstruction, primary and secondary biliary cirrhosis and infectious hepatitis.

Studies with the preparative ultracentrifuge

TABLE 38. COMPARISON BETWEEN THE AVERAGE PHOSPHOLIPID AND FREE CHOLESTEROL CONCENTRATIONS IN THE LIPOPROTEIN FRACTIONS ISOLATED BY ALCOHOL PRECIPITATION FROM THE SERA OF 7 PATIENTS WITH BILIARY CIRRHOSIS
(Eder and associates)

	PLASMA	α LIPO- PROTEIN FRACTION	β LIPO- PROTEIN FRACTION
Phospholipid	1319	949	364
Free Cholesterol	616	451	161
Total Cholesterol	700	456	241

in the author's laboratory have demonstrated that the lipoproteins from these sera are of very high molecular size. Clear lipoprotein fractions could be obtained by ultracentrifugation in 1 molar sodium chloride solution, which contained as little as 20 per cent protein, the free cholesterol and phospholipid making up the greatest part of the lipoprotein. Thus the lipids from these sera are bound to protein in such a way that they are made uniquely soluble in aqueous solution, as was suggested by the unusual clarity of the whole sera of these patients.

The phospholipids consist almost entirely of lecithin, and the high concentration of this hydrophilic lipid certainly plays a major role in producing these soluble lipoproteins. Observations with the enzyme lecithinase indicated that with the splitting of lecithin, cholesterol also became insoluble.[2] Recent work has implicated the bile acids as factors in the elevated lipid levels in the sera of animals with obstructive jaundice,[6] and this also may apply in humans. Injection of sodium cholate into rats with biliary obstruction and into rats with unilateral nephrectomy raised the cholesterol levels of the serum considerably;[6] even normal rats showed some elevation of cholesterol following this procedure. Another surface-active agent, triton WR-1339, produces great elevation of cholesterol in normal rats and rabbits following infection.[25] Interestingly, the phospholipids show an even greater rise, and an analogy to the situation in biliary obstruction is apparent. These observations raise the possibility that the bile acids form a part of the unusual lipoprotein complex found in the serum of the patients under discussion. The lack of adequate methods for determining the bile acids has hampered progress in the solution of this problem.

It is of some interest that these patients do not appear to develop unusual deposition of lipid in their arteries, despite the serum lipid abnormality and definite deposition of lipid in the skin and the tendon sheaths. The reason for this is not entirely clear but appears to be related to the unusual soluble state of the lipoproteins. Many factors undoubtedly are involved in the formation of xanthomata, but their appearance depends primarily on the degree and the duration of the lipid abnormality in the serum, and it
has been possible to relate, approxima
the extent of lipid deposition and the se
lipid level.[3] Levels of total lipid of 1,800
per cent or more usually precede the d
opment of widespread flat or tuberous
thomata. Levels of 1,300 to 1,800 mg.
cent are commonly found in patients
xanthelasma alone. Lipid levels below 1
mg. per cent do not appear to be relat
any lipid changes in the skin. The dur
of the lipid alteration in each patient is
a very important factor and is usually
cult to define. Certainly the lipid abnorm
must persist for several months. Alth
these relationships are not exact to an
gree, it has been possible to predict th
velopment of xanthomata in several pa
on the basis of the serum lipid abnorma
In addition, sustained elevated levels a
to require a considerable amount of
tioning liver tissue, and with progressi
the cirrhotic changes in patients with b
cirrhosis a fall in lipids usually occur
variably, this is associated with resolutio
disappearance of most of the xantho

THERAPY

Despite recent progress in delin
primary biliary cirrhosis as a common
curring condition with certain charact
features, it still appears advisable to ex
the extrahepatic biliary system at lapar
to rule out an obstructive lesion in each
No specific therapy for primary biliar
rhosis exists, and this makes it all the
important to rule out completely a seco
biliary cirrhosis, even if the possibiliti
remote. In those rare cases of primary
cirrhosis where an etiologic factor su
arsenic is apparent this medication c
discontinued, although this probably d
tle except prevent further injury. Re
phlebotomies with reinjection of the
removed are probably of value where
chromatosis is the underlying etiologic

The major therapeutic efforts in p
biliary cirrhosis are directed toward
taining the patient in a fairly useful s
preventing the complications that fre
ensue. Many of these patients are
lead fairly normal lives for periods
as 10 or 15 years after the onset. No

has been proved to be of value. Very protein diets are unnecessary: from 75 00 Gm. of protein is adequate. Dairy up to 100 gm. per day should be given. t of the patients do not show an intol- ce to fatty food, and restriction is un- ssary. Bed rest appears to be of little e, and the patients seem to get along well out curtailment of activity. It is impor- to supplement the diet daily with fat- ble vitamins because of the spruelike pic- (vitamin A, 4,000 units; D, 1,000 units; mg.). Bleeding episodes have been ob- ed that have responded dramatically to nin K. Intravenous calcium and vitamin pplementation appear to be of value in enting the frequently observed osteoma- . A tendency to diarrhea produced by large soap content of the stools can be come by bulk laxatives such as methyl lose. Bile salts have proved to be of use.

he relief of itching is one of the major peutic problems in these patients, and reatment available is still unsatisfactory. he author's experience methyl testoster- has been the most effective agent avail- Unfortunately, an increase in jaundice lly occurs during this therapy. The bili- n usually returns to the original levels essation of therapy, and no deleterious ts have been apparent. However, this tion is not settled completely; the itching ese patients is sometimes so bad that in hazards must be taken. In addition s effects on itching, methyl testosterone sometimes lowers the cholesterol and pholipid levels in the serum after pro- ed therapy and may reverse the process anthoma formation. Cortisone has also advocated for the relief of itching. H has not been of value in the author's experience, and thrombotic complications were observed in one patient with primary biliary cirrhosis.

Eventually, the majority of patients with primary biliary cirrhosis develop esophageal varices and hemorrhages into the gastrointestinal tract, and the question of subjecting these individuals to a portacaval shunt arises. In the author's experience 4 patients with primary biliary cirrhosis have had this operation. One woman died 1 week after operation. She had a serum bilirubin level of 12 mg. per cent preoperatively that rose precipitously after the procedure. The other 3 cases were benefited. One patient (Patient 2 reported by Ahrens and associates[3] and Patient 1 of Ricketts and Wissler[41]) died 4½ years after operation, chiefly of cholemia without further hemorrhage or ascites. She had led a comfortable and active life for several years after operation, although close to death on several occasions as a result of massive hemorrhages prior to the shunt. The 2 remaining patients have been followed 2½ and 3 years after operation and have been free of hemorrhages, which in each case had been present initially. Both patients now have higher bilirubin levels, suggesting a continuous progression of the disease. The operation appears to be of little value other than to prolong the life of the patient by preventing hemorrhages.

The treatment of secondary biliary cirrhosis which is primarily surgical will not be considered in this review. The medical treatment involved is usually similar to that for primary biliary cirrhosis. The improvement of secondary biliary cirrhosis following surgical relief of the obstruction is usually surprisingly great, and surgery is indicated, regardless of how severe the liver damage is thought to be.

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Chapter 17 HEMOCHROMATOSIS

Theodore L. Althausen, M.D.
and Victor M. Sborov, M.D.

Hemochromatosis was first described by Trousseau in 1865.[47] Since that time approximately 500 cases of this disease have been reported in the literature.[29] Despite its relative rarity, hemochromatosis has intrigued clinicians and investigators far out of proportion to its statistical importance. Numerous publications have recorded case histories, physical findings, histologic changes, laboratory data, studies of metabolism, and other aspects of this disease. Even single case reports, whose only purpose is to call attention to some hitherto undescribed feature of hemochromatosis, are not uncommon in the literature. There are two principal reasons for the great interest in this condition: First, a gross perversion of iron metabolism is involved, the study of which promises to shed light on normal iron metabolism. Second, the patient with hemochromatosis often manifests both diabetes mellitus and hepatic cirrhosis, a rare combination which offers unusual opportunities for studying the activities of both the pancreas and the liver, especially in regard to carbohydrate metabolism.

The early detailed descriptions of its clinical manifestations, the many speculations regarding its etiology, and the gradual improvement in diagnostic methods make up one important part of the history of hemochromatosis. Overshadowing these in practical importance are the various therapeutic regimens which have been tried and their success in prolonging the lives of the patients and in altering the clinical manifestations of this disease.

Three milestones mark the outstanding advances in the therapy of hemochromatosis. The first, undoubtedly, was the introduction of insulin and its use in the control of
betes mellitus, a member of the classic
formerly needed for the diagnosis of he
chromatosis.[2] Early enthusiasm regarding
efficacy of insulin in ameliorating the co
of the disease and lightening the skin
mentation in hemochromatosis were dim
when it was found that despite such ther
the disease progressed and the patients
from other complications. The importanc
insulin in the management of these pati
is undeniable, but the hypothesis that it a
the fundamental mechanisms of hemoc
matosis and halts its progress is no lo
tenable. In the late 1930's and early 19
when the introduction of dietary meas
proved to be successful in the manage
of chronic liver disease, it was hoped
similar measures would further improve
prognosis in hemochromatosis. Unfo
nately, this approach has made only a mo
contribution toward improving the outlo
this disease.

The application of modern research
nics to the problem of iron metabolism i
past 15 years has resulted in a fundam
understanding of the absorption, the ut
tion, the storage and the excretion of
by the human body.[22] The natural exte
of this knowledge to therapy has result
procedures which under favorable cir
stances permit removal of large amoun
iron from the tissues of patients suff
from hemochromatosis.[13, 14, 29] This
ment is followed by definite improveme
general well-being, strength and abilit
work and in the clinical and the labor
manifestations of pancreatic and he
function. Thus, with modern methods

nosis, both histologic and biochemical, and ith current means of therapy, the present itlook for the patient with early manifes- tions of hemochromatosis is relatively opeful.

INCIDENCE

Because of the widespread interest in this sease, it is probable that an unusually large oportion of recognized cases have been ported. Of 240,000 patients admitted to e University of California Hospital through 952, 36 were diagnosed as having hemo- romatosis. Mallory reported 3 instances of is disease in 6,000 autopsies, and it was und 4 times in 5,000 autopsies at Bellevue ospital.[46, 47] That the diagnosis is more ommon in the morgue than in the clinic obably can be attributed to difficulties in e recognition of the disease during life. owever, Butt and Wilder,[12] in a study cov- ing a 15-year period at the Mayo Clinic, ported 30 cases in which the diagnosis was ade during life, and one of us (T.L.A.) as able to study 15 patients with this dis- se during a sabbatical leave in Melbourne, ustralia.[4]

Statistics show by far the greatest incidence hemochromatosis in males. It occurs be- een the ages of 35 and 60 years, reaching peak between 45 and 50 years. Well- thenticated cases of hemochromatosis in males also have been described.[29, 47] Of the tal 540 cases reported in the literature, ly 30 occurred in women. Women as a le develop the disease later in life than en. The fact that the disease is diagnosed ost often in women past the menopause is some importance in view of current con- pts of the excretion of iron by the human dy.

Familial cases of hemochromatosis have en described.[4, 47] In some cases the relatives patients with frank hemochromatosis have d similar abnormalities of the serum iron ncentration and of the saturation of iron- nding protein. In one series of 15 cases[4] diagnosis of hemochromatosis was estab- hed in a brother of one of the female pa- nts and of one of the males. In this same oup a family history of excessive pigmenta- n was found in 4 cases, of diabetes in 4, d of hepatic disease in 3. Other authors have made similar observations. For instance, in 12 of 30 cases described by Marble and Bailey,[37] diabetes was known to occur in some relative, although there was no family history of hemochromatosis. Conversely, in a study of approximately 30,000 newly diagnosed cases of diabetes mellitus, Marble and Bailey found hemochromatosis in 0.16 per cent. The hereditary pattern of hemochromatosis, although obscure at the present time, should be borne in mind, since it may provide important clues to the etiology of this disease.

CLINICAL FEATURES

History

Since hemochromatosis is a multiple system disease, it is manifested by a wide variety of symptoms. These symptoms can be divided into those which are nonspecific or general in nature and those which relate to some organ system of the body. The outstanding general symptoms are weakness, fatigability and lack of energy and initiative; loss of weight also may occur. These symptoms, which are found in varying degrees in all patients with clinically demonstrable hemochromatosis, are gradual in onset, but progressive; in many instances they have been noted to persist despite therapy for diabetes and for hepatic disease. Frequently, these general complaints antedate the diagnosis of the disease by many years.

The major manifestations of the disease consist of the classic triad of pigmentation of the skin, diabetes mellitus and cirrhosis of the liver. This triad was noted at the time of diagnosis in over 80 per cent of the cases described in the literature.[47] Because more specific diagnostic procedures were not available until quite recently, it is understandable that these 3 manifestations were seen in such a large proportion of the reported patients, since, by definition, they comprise the clinical syndrome of hemochromatosis. However, it is to be anticipated that with current diagnostic technics, the disease will be recognized at an earlier stage, and many patients will lack the classic triad when they first come under medical observation.

Increased pigmentation usually is not complained of by the patient; its presence and the details concerning its development must be established by careful interrogation.[7] The time at which the increase in pigmentation began can rarely be fixed exactly. As a rule, the patient is only aware that his skin has been dark for a number of years, sometimes for decades, and has become darker in the period immediately preceding medical observation.[47]

In contrast, the onset of the symptoms of diabetes mellitus, particularly polydipsia and polyuria, can be established with relative exactness. These latter symptoms, along with weight loss which usually is related to the diabetes mellitus, generally can be controlled without difficulty by means of diet and insulin.[8, 12]

In hemochromatosis the principal symptoms related to the liver are hepatic enlargement and tenderness; jaundice and ascites are much less frequent. Anorexia, diarrhea and other gastro-intestinal symptoms, which also may be related to involvement of the liver, are often present.

Symptoms referable to the cardiovascular system, such as arrhythmias, palpitation, exertional dyspnea, orthopnea, ankle edema and angina pectoris, have been recorded in this disease.[26] No correlation has been found between the type and the severity of the cardiovascular manifestations and the presence and the extent of hemosiderin deposits in the myocardium. For this reason it is often difficult to determine whether these symptoms result from the hemochromatosis or from a co-existent cardiovascular disease.

Impotence and lack of libido are frequent complaints among patients with hemochromatosis.[3] Whether they are manifestations of hepatic insufficiency or of malnutrition has not yet been demonstrated clearly. Possibly they result from hypogonadism, since other manifestations of hypogonadism have been demonstrated in many of these patients.[47]

PHYSICAL EXAMINATION

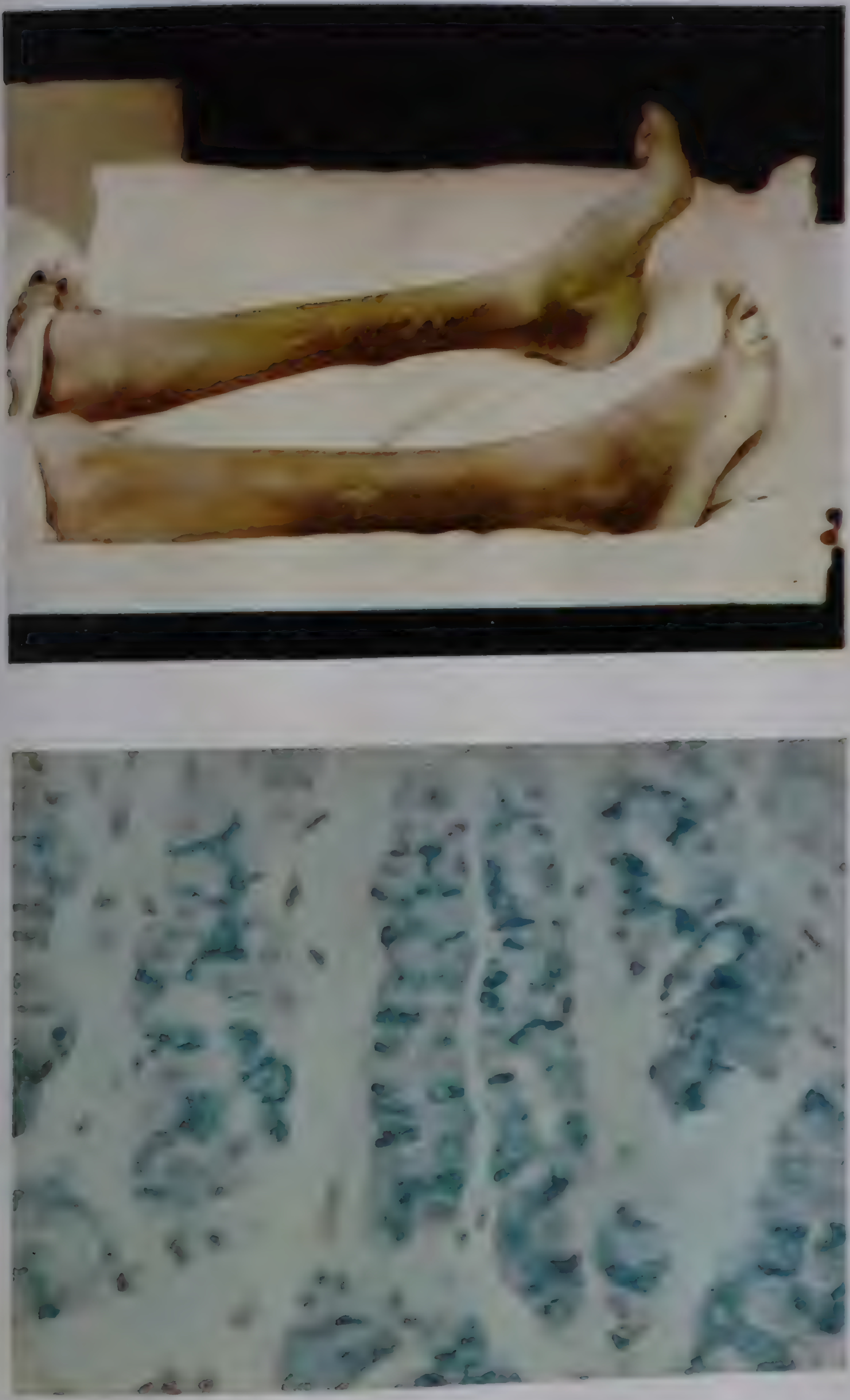
Pigmentation of the skin and the mucous membranes, one of the classic triad of symptoms, should draw the attention of the physician immediately to a possible diagnosis of hemochromatosis. The pigmentation usually considered as characteristic of hemochromatosis is "bluish gray" or "slatey" in
color, as distinguished from a more c
generalized brown pigmentation w
also present (Plate 2). Both types of
tation in our experience appear pro
on the forearms and somewhat les
the face, the neck, the arms, the h
legs and the feet.[4] Distribution of th
gray pigmentation is sometimes ge
but even then is more prominent on
mentioned. However, Sheldon found
mentation more abundant in the axi
the inguinal folds and around the ge
The nature and the distribution of
mentation seem to be too variable t
tute a pathognomonic sign, especia
slatey tint is missing.

Pigmentation of the mucous me
is also common, as evidenced by S
report of this finding in 16.7 per ce
collected patients with hemochro
The mucous membranes of the mo
ticularly the inside of the cheeks, are
sites for pigmentation. The pigmen
occurs in localized plaques or are
than in generalized deposits. Pig
has been found also in the conjunc
at autopsy, in the trachea, the esoph
the stomach. The depth of pigmen
variable, even in untreated patients.
ening of the pigmentation has be
after bouts of alcoholism, incident
vation of diabetes, and in the termi
of the disease.[47] Conversely, dimi
pigmentation has been observed r
following the use of insulin in pat
previously uncontrolled diabetes.
reason for this decrease is not clea

The skin of patients with hemoc
sis usually is shiny and dry or scal
tion of the skin in such cases reve
texture with considerable atrophy.

The liver is involved in all cases
chromatosis; in fact, enlargement o
can be regarded as the most consta
feature of this disease. Characteris
liver is massively enlarged, hard,
and in some instances tender. Us
enlargement is diffuse, affecting bot
and the left lobes, although cases h
noted in which the left lobe w
enlarged, while the right lobe w
volved. The liver also has been de
coarsely nodular on palpation. T

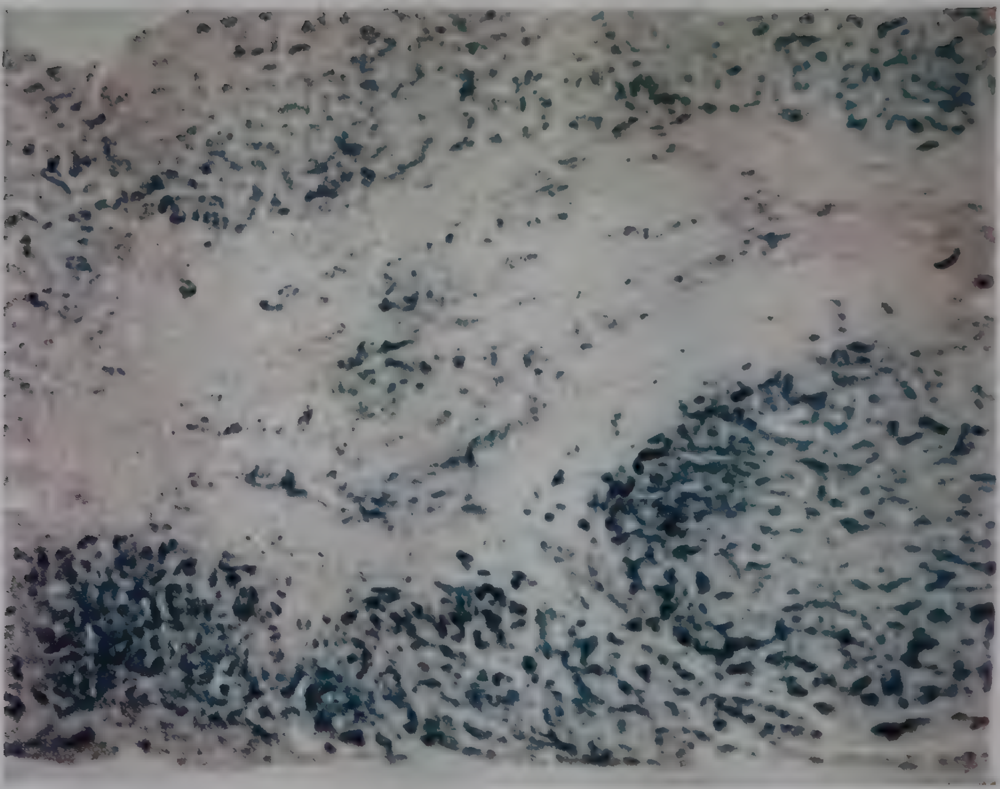
PLATE 2



(A, *Top*). Characteristic melanosis of the skin in hemochromatosis. (Althausen, T. L., and Kerr, W. J.: Endocrinology 11:377-422.)

(B, *Bottom*). Biopsy specimen of gastric mucosa from a patient with hemochromatosis. Chief cells of tubular glands are laden with hemosiderin, while the parietal cells are practically free of this pigment (ferric ferrocyanide and hematoxylin, × 450). (Althausen, T. L., et al.: A. M. A. Arch. Int. Med. 88:553-570.)

PLATE 2 (*Continued*)



(C, *Top*). Biopsy specimen of liver from a patient with hemochromatosis before treatment with multiple phlebotomies. Extensive portal cirrhosis is present, with massive deposition of hemosiderin in the polygonal and reticuloendothelial cells (ferric ferrocyanide and hematoxylin. × 200).

(D, *Bottom*). Biopsy specimen of liver from the same patient as in C, taken after removal of 37,000 cc. of blood in a 14-month period. Portal fibrosis persists unchanged despite the almost complete removal of iron from the liver (ferric ferrocyanide and hematoxylin. × 200).

palpable in about 50 per cent of cases. inical jaundice is quite rare.[12] Ascites is a irly frequent complication, particularly iring the later stages of the disease. Spider vi and superficial ecchymoses also occur a moderate number of patients with hemo- romatosis. Bleeding from rupture of ophageal varices has resulted in death in me cases. Use of modern roentgenologic ethods and esophagoscopy probably will monstrate esophageal varices in a rela- ely large number of patients with hemo- romatosis.[11]

Myocardial involvement, evidenced by ar- ythmias and symptoms of congestive heart lure, has been described in this disease. orns,[28] in a review of recent English and nerican literature, noted 9 cases of hemo- romatosis in which cardiac symptoms and ns were prominent. In 6 of these cases topsy revealed extensive deposits of hemo- lerin in the myocardium. Three of the 6 tients had suffered severe precordial pain th typical radiation; in 2 cases it was so ense that coronary occlusion was sus- cted, although it could not be proved at topsy. According to Horns, the most com- on electrocardiographic change in these tients was low voltage. Complete heart ock was noted in 2 cases, and auricular rillation in 2. The relative rarity of symp- ns and objective findings indicative of my- ardial involvement in the recorded cases is prising in view of the extensive hemo- erin deposits found in the myocardium of actically all patients examined postmortem.

The body hair of patients with hemochro- tosis is characteristically sparse, soft and n.[4] In men the body hair may show a ninine distribution. Whether the hair anges are caused by the disease or whether nochromatosis is more common in indi- uals with hair of this type and distribution not known.

In one group of 20 male patients more n one half had atrophic or soft testicles, l in some cases a small penis.[47]

IRON METABOLISM

In the past several years much investiga- e effort has been directed toward accumu- on of fundamental information concerning the handling of iron by the human body. Certain concepts have been developed, which although not yet finally established, have served to clarify our understanding of iron metabolism.[38] Granick[22] demonstrated that normally iron is absorbed from the gastrointestinal tract in the region of the duodenum and, more specifically, in the area just distal to the pyloric sphincter. When large amounts of iron are ingested, more extensive portions of the small intestine probably participate in this function. It has been shown that iron is absorbed most readily when in the ferrous form and that its absorption is influenced by local environmental conditions. For instance, achlorhydria, alkaline medications and diets high in phosphorus content are known to decrease the absorption of iron from ingested food.[53]

According to Granick,[23] the ingested iron becomes bound to a protein acceptor, called apoferritin, which is present in limited amounts in the intestinal mucosa. The combined form, known as ferritin, releases the iron to the plasma; then the apoferritin is again capable of combining with ferrous iron. Granick postulated that the apoferritin-ferritin system regulates the absorption of iron from the gastro-intestinal tract by blocking further uptake when the available apoferritin is combined with iron (Fig. 143 A).

In the plasma, the nonheme iron is bound to a protein called siderophilin and circulates in this combination.[43] Siderophilin is a beta$_1$ globulin which binds not only iron but copper and zinc as well.[50] The total iron-binding capacity of normal serum is approximately 300 micrograms per 100 cc. of blood; usually, however, only approximately one half of this capacity is utilized.[21, 30] In hemochromatosis serum iron levels as high as 480 micrograms have been reported.[4] The level of serum iron usually reflects the amount of iron available for the synthesis of hemoglobin.[22, 31] This level does not regulate the movement of iron from the intestinal mucosa into the blood.[49]

Iron cannot circulate in the blood in the free state except in patients in the terminal stages of hemochromatosis or in persons given massive amounts of iron intravenously.[22] The complete binding of iron to protein, both in the blood and in the tissues, is believed to account for the exceedingly small amounts of iron normally lost from the human body. The daily loss of iron in the urine varies from 0.1 to 1.3 mg., according to different investigators;[52] in addition, minute amounts are lost in desquamated cells of the skin. Small amounts of iron also reach the gastro-intestinal tract in the bile and other digestive secretions but are subject to reabsorption.

In the normal individual from 75 to 85 per cent of the total body iron is contained in the hemoglobin of the red blood cells and muscle, 15 per cent (in the form of ferritin) is stored in the gastro-intestinal tract, the liver and the spleen, and approximately 1 per cent is contained in the heme enzymes of the cells.[22] The average diet provides from 5 to 15 mg. of iron daily, of which approximately 0.5 mg. is absorbed. In idiopathic hemochromatosis, failure of the duodenal blocking mechanism results in the taking up of excessive amounts of iron. This has been elucidated clearly by the use of iron-balance technics. Using small amounts of radioactive iron ingested in the ferric form, Peterson and Ettinger[41] found the normal absorption of iron from the gastro-intestinal tract to be 1.5 to 4.4 per cent. In patients with hemochromatosis, on the other hand, from 20 to 45 per cent of the ingested iron was absorbed. It was shown further that the uptake of radi active iron in the red blood cells cannot used as an index of iron absorption in p tients with already increased iron stores. T authors concluded that the only reliable w to measure iron absorption is by the balan technic. Other studies[1] have confirmed t fact that the amount of radioactive iron the circulating red blood cells cannot be us as an index of iron absorption.

Studies by Gitlow and Beyers[20] indica that in hemochromatosis not only the int tinal mucosa but other tissues as well a parently develop a greater affinity for ir The consequent gross overloading of the ir depots of the body which takes place ov a period of many years eventually results the clinical manifestations of this disea Whereas the total body iron normally is ab 4.5 Gm., in patients with hemochromato it may amount to more than 50 Gm. T iron, in the form of hemosiderin, a fer hydroxide polymer which microscopically h the appearance of granular brown partic is deposited in most of the tissues of the b in hemochromatosis.

The available facts indicate that a grea than normal absorption of iron over a per of years is responsible for the final pict of massive iron deposition in the tissues the patient with hemochromatosis.[4, 5] Si

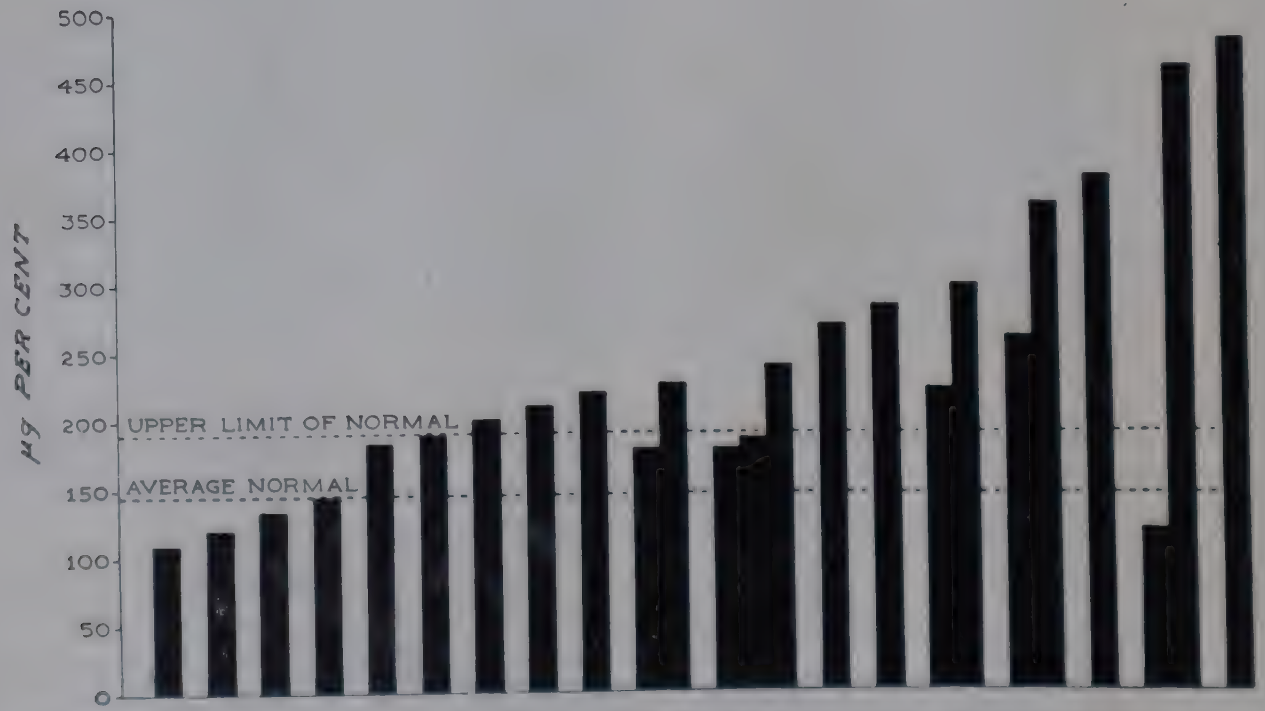


FIG. 141. Serum iron levels in 18 patients with hemochromatosis. (Althausen, T. L., et al.: Tr. A. Am. Physicians 63:209-218)

only very small amounts of iron are lost normally, except during menstruation and as a result of pregnancy, this disease can be controlled only (1) by blocking absorption of iron and (2) by removing excess storage iron by repeated withdrawal of red blood cells[14] or increasing the elimination of iron through normal channels.[55]

LABORATORY FEATURES OF HEMOCHROMATOSIS

Serum Iron

The serum iron level is a valuable aid in the diagnosis of hemochromatosis. Althausen and co-workers[4] found abnormal serum iron levels in 12 of 18 cases of proved hemochromatosis (Fig. 141). Serial determinations in 5 of the 18 cases after an average interval of 15 months showed a significant increase in each case.

According to Houston and Thompson,[30] a considerable rise in serum iron levels occurred after the oral administration of 1 Gm. of ferrous sulfate to normal subjects. However, in 7 cases of hemochromatosis in which fasting serum iron levels were high, these authors found little or no rise in iron levels after the ingestion of ferrous sulfate.

Although the concentration of iron-binding protein in the blood is not changed in hemochromatosis, the percentage of this protein saturated with iron is very high. Houston and Thompson[30] found it to be approximately twice as high in patients with hemochromatosis as in normal controls.

A test for determining the iron-binding capacity of the blood has been described by Rath and Finch.[43] The method is based on the observation of Schade that beta_1 globulin, which is colorless, assumes a salmon-red color when it combines with iron. When this protein becomes saturated with iron, the color curve shows a sharp break at the exact point where free iron can be demonstrated by bio-assay. As previously noted, no significant increase in serum iron concentration follows oral or intravenous administration of iron to patients with a saturated iron-binding capacity such as occurs in hemochromatosis.[30]

Hepatic Function

In hemochromatosis a surprising lack of correlation exists between impairment of liver function and both structural changes and hemosiderin deposits in the liver. Butt and Wilder[12] reported that liver function was

Table 39. Results of Liver Function Tests in 15 Patients with Hemochromatosis

		Thymol						
Case No.	Cephalin Flocculation	Flocculation	Turbidity, Units	Gamma Globulin, Gm./100Cc.	Serum Albumin, Gm./100Cc.	Hippuric Acid Synthesis, Gm.	Bromsulphalein Retention, 45 Min., %	Liver Biopsy Specimen
1	0	0	6	1.03	5.5	0.42	10	Hemosiderin only
2	0	0	4.6	1.05	4.8	0.82	5	Hemosiderin only
3	0	0	5	1.30	5.2	0.72	5	Multinodular cirrhosis
4	0	0	3.5	1.03	4.7	0.22	5	Multinodular cirrhosis
5	0	0	5.5	1.26	4.0	0.59	5	Hemosiderin only
6	++	0	12.5	1.32	3.9	0.42	20	Multinodular cirrhosis
7	+	0	8	1.43	4.3	0.23	10	Multinodular cirrhosis
8	0	0	7	1.35	6.4	0.20	10	Multinodular cirrhosis
9	0	0	7	1.30	3.9	0.79	20	Multinodular cirrhosis
10	0	0	5.2	. . .	4.0	0.80	7	No biopsy
11	+	0	8.6	1.12	6.2	0.97	. .	Multinodular cirrhosis
12	0	0	7.3	1.21	6.2	0.22	5	Laennec cirrhosis
13	0	0	9.5	1.49	4.8	0.33	15	Laennec cirrhosis
14	0	0	6.5	1.13	5.2	0.39	5	Multinodular cirrhosis
15	+	0	9.6	1.52	4.3	0.29	5	Multinodular cirrhosis
Normal	0 to +	0	<5	<1.24	>4	>0.7	<5	

(Althausen, et al.: Arch. Int. Med. **88**:553-570, 1951)

TABLE 40. RESULTS OF PANCREATIC FUNCTION TESTS IN 15 PATIENTS WITH HEMOCHROMATOSI

Case No.	Rise in Amino Nitrogen of Blood, Mg./100 Cc.		Duodenal Contents After Secretin		
	After Gelatin	After Glycine	Volume, Cc.	Bicarbonate Concentration, mM./Cc.	Total Bicarbonate, mM.
1	3.6	3.8	107	0.110	11.7
3	2.7	. .	350	0.060	21.1
4	2.2	6.4	187	0.038	6.4
5	6.3	. .	. . . .	. . . .	
6	1.7	3.4	. . . .	. . . .	. .
7	3.7	. .	. . . .	. . . .	. . .
8	4.1	. .	223	0.064	14.4
9	3.5	. .	. . . .	. . . .	.
11	2.0	. .	. . . .	. . . .	. . .
12	0.5	3.2	333	0.072	24.8
13	0.9	4.1	166	0.093	15.4
14	1.6	3.0	480	0.052	25.4
15	1.8	4.6	. . . .	. . . .	. . .
Normal range	2.0	2.5	90–192	72–128	10.7–17.75

(Althausen, et al.: Arch. Int. Med. **88**:553-570, 1951)

often within normal limits in their patients. In another comprehensive study of 15 patients,[4] hippuric acid synthesis was found to be depressed in two thirds of the cases, while bromsulphalein retention and gamma globulin levels were abnormally high in one half of the cases. Other manifestations of hepatic insufficiency occurred in an even smaller proportion of patients (Table 39). These data indicate a lesser degree of hepatic insufficiency in hemochromatosis than in other forms of cirrhosis with a comparable degree of fibrosis. A slower progress of the fibrosis may account for this difference.

PANCREATIC FUNCTION

The exocrine function of the pancreas was studied in 13 patients with hemochromatosis[4] (Table 40). In 5 of these patients the ability to break down gelatin apparently was impaired, probably due to insufficient secretion of trypsin. A secretin response test was performed in 7 patients in this group; in only one case was the total amount of bicarbonate secreted lower than that secreted by control subjects, while 4 of the patients showed hypersecretion of a dilute pancreatic juice.*

The laboratory features of diabetes i hemochromatosis are quite variable. In man cases the presence of diabetes mellitus ca be detected only by means of the glucose to erance test;[12] in others, frank diabetes apparent. Both insulin-sensitive and insulin resistant types of diabetes have been noted this variation may result from involvement other organs which influence carbohydrat metabolism, such as the liver, the pituitar and the adrenals.

THE BLOOD

Anemia was reported by earlier obser ers[47] to be a prominent feature of hem chromatosis; subsequent investigators we unable to confirm this finding.[46] Studies the other formed blood elements have show only inconstant deviations from normal.

ETIOLOGY AND PATHOGENESIS

Through the years a number of hypothes have been proposed to explain the abnorm accumulation of iron in the tissues of variou organs and the pathophysiology of the clinic manifestations in hemochromatosis. Wha ver hypothesis one entertains, it must be onsistent with the concept that the disease evelops over a period of many years. In atients with hemochromatosis the amount f iron in the tissues varies from 10 to 50 Gm.[13] Even if the entire 5 to 15 mg. of iron sually contained in the diet were absorbed ach day, it would take from 6 to 30 years to ccumulate the large deposits present in the issues of patients with hemochromatosis. This is all the more true since it is highly nlikely that intestinal absorption of iron is ver complete.[46]

---

* Dreiling,[15] in a study of 71 patients with chronic inflammatory disease of the pancreas, reported this same finding in the only patient with hemochromatosis. It is of interest that the only other patient in this series who secreted an unus ally large volume of pancreatic juice had "pa creatic fibrosis and hepatic cirrhosis" shown biopsy.

One of the earliest and most attractive heories, even today, is that excessive hemolyis of red blood cells in hemochromatosis berates iron, which is deposited in the tisues of the body.[18, 47] It is known, for exmple, that in untreated pernicious anemia, emolytic anemias and refractory anemias inreased amounts of iron often are found in he liver and other tissues of the body, even vhen no blood transfusions have been given. number of possible explanations for such emolysis have been advanced; however, depite careful studies of pigment metabolism nd red cell turnover, an excessive destrucion of red blood cells in hemochromatosis as not been proved.

In spite of the negative outcome of these studies, the red blood cell is undoubtedly one of the most logical sources of iron. Indeed, several recent reports describe a form of hemochromatosis of exogenous origin following multiple blood transfusions to anemic patients.[46, 53] It is also true that in anemia the uptake of iron from the gastro-intestinal tract is increased.[16] Thus, the excessive deposition of iron in anemic individuals may result from a combination of factors, rather than from a single factor. The frequent occurrence in South African natives of another exogenous form of hemochromatosis of dietary origin has been described by Gilman and Gilman.[19] These authors also observed features of this disease in patients with pellagra and other forms of malnutrition due chiefly to a staple diet of corn. They concluded that this form of hemochromatosis is caused by a derangement of metabolism which finally results in widespread dissemination and deposition of iron pigment in the tissues. They stated that the concomitant hepatic cirrhosis is not necessarily the result of the deposition of iron in the liver but may have been preexistent or due to other causes.

The nutritional hemochromatosis described by the Gilmans is now thought to be related to a disturbance of the iron-phosphorus ratio in the diet, whereas the fatty and fibrous tis-

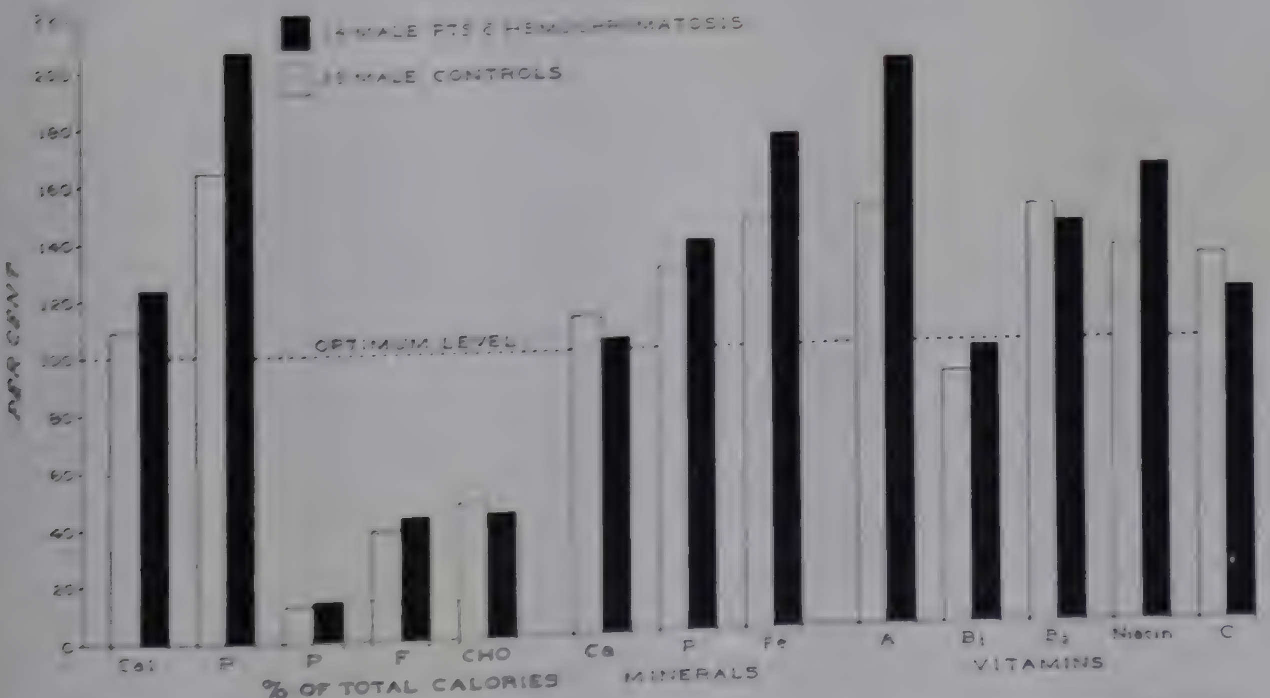


FIG. 142. Dietary intake in per cent of optimum amount recommended by National Research Council compared in 14 male patients with hemochromatosis and 25 male controls. (Althausen, T. L., et al.: Tr. A. Am. Physicians 63:209-218)

sue changes seen in the livers of the South African natives with this condition may be the manifestation of an independent nutritional liver disease.[19] Hegsted and his co-workers[26] demonstrated that rats fed a diet low in phosphorus with liberal additions of iron will develop an increase in iron absorption and storage. A similar situation exists in South Africa, where a high dietary intake of iron with a very low proportion of phosphorus favors excessive absorption of iron. A recent detailed survey of a group of patients by Althausen and co-workers[4] showed no deficiency in the phosphate intake and only slightly increased iron content of the diet (Fig. 142).

Knutsen[35] suggested that hemochromatosis results from a primary cirrhosis of the liver and the pancreas which leads to an abnormality of iron metabolism and a progressive deposition of iron in the tissues. He also postulated that the formation of the related iron-free pigment, hemofuscin, also present in the tissues of patients with hemochromatosis, stems from an abnormality of sulfur-protein metabolism caused by hepatic dysfunction. This hypothesis is partially supported by the fact that markedly elevated serum iron levels are known to occur in acute viral hepatitis and in some cases of chronic liver disease.[40]

Sheldon[47] concluded that hemochromatosis results from a congenital endogenous disturbance of the intermediary metabolism of iron which manifests itself partly by the formation of iron-containing hemosiderin in the tissues and partly by the formation of iron-free melanin in smooth muscle, connective tissue and skin. At one time Mallory advanced the hypothesis that copper poisoning causes hemochromatosis. He and his co-workers[36] produced cirrhosis of the liver with pigmentation of several parenchymatous organs resembling that of hemochromatosis by feeding large amounts of copper acetate to animals. In addition, they were able to elicit a history of industrial exposure to copper from several patients with hemochromatosis. Herkel[27] found that the livers of patients dying from hemochromatosis contained greatly increased amounts of copper, although the same was true of patients with hepatic cirrhosis and normal infants. Although one group of investigators was able to confirm the animal experiments of Mallo et al., several other workers were unable do so.[8] Mallory's theory was widely accept for a time but was gradually abandoned wh it became apparent that few patients w hemochromatosis had been exposed to co per, and that relatively enormous amou of copper were required to produce hepa lesions in experimental animals.

Once alcoholism was considered as an i portant contributing cause of hemochrom tosis, particularly since a large proportion reported cases occurred in chronic alcoholi For instance, in a series of 61 cases collect by Bork[10] almost two thirds of the patie were classified as alcoholics. However, t occurrence of hemochromatosis in total a stainers shows that alcohol cannot be the o cause of this disease.

Current information concerning iron m tabolism in the normal state, in hematolo disorders and in hemochromatosis indica that a fundamental defect underlies the creased absorption of iron from the gast intestinal tract in patients with hemochrom tosis.[1, 16, 41] The cause of this increase and exact mechanism involved are as yet un termined. The increased absorption of ir plus the lack of a natural mechanism for creting excesses of iron from the body, counts for the widespread deposition storage of iron pigment in the tissues and resultant secondary changes in their struct and function.

Considerable controversy has stemm from attempts to differentiate between hem chromatosis and hemosiderosis.[5, 33] Some vestigators regard them as two distinct e ties with different clinical and prognostic plications.[25, 33, 39] Numerous transfusions a administration of large amounts of iron mouth or by vein to patients with anem sometimes result in excessive deposition iron in the tissues; this has been term hemosiderosis. The once-popular belief t storage of such massive amounts of iron the tissues did not interfere with their fu tion has not been substantiated. On the c trary, cases of so-called hemosiderosis of ogenous origin which are clinically in tinguishable from classic hemochromato have been reported recently.[9, 46, 53] Such patient with exogenous hemochromatosis udied recently by us at the University of alifornia Hospital. The patient was a 59-ear-old white male who was first studied in ew Zealand. He enjoyed good health until years before his present admission, when e sought medical help for an anemia. After areful studies, including the finding of a ypoplastic bone marrow, the diagnosis of plastic anemia was made. In the following -year period he required over 300 units of hole blood to maintain a satisfactory hemolobin level. In addition, he received supporve therapy which included 0.9 Gm. of ferous sulfate daily during this entire period.

While under medical observation the paent's liver and spleen had enlarged gradally in the past 2 or 3 years. Shortly before e present hospital admission he noticed that is skin had become slate gray in color. There as no history of jaundice, ascites, weakness r symptoms suggestive of diabetes mellitus. . liver biopsy 6 months prior to the present ospitalization was reported to show "cirrhos and hemosiderosis."

Physical examination revealed a modertely obese white male in no distress. No undice was present. A slate gray and rownish pigmentation was noted over the dorsum of the hands, the face and the exposed portion of the neck. The distribution of the body hair was normal. Blood pressure was 158/82. The heart was not enlarged. The heart rate was normal, and no cardiac arrhythmia was present. The liver was enlarged to 8 cm. above and 10 cm. below the right costal margin in the mid-clavicular line. The spleen was palpated 6 cm. below the costal margin. The liver and the spleen were firm and not tender. The testicles were small and atrophic.

Laboratory studies for hemosiderin in urinary sediment were negative. A urinalysis was normal except for 2 plus albuminuria. A sternal bone marrow aspiration showed a hypoplastic marrow with abundant deposits of hemosiderin. Results of the following tests were within normal limits: prothrombin time, thymol turbidity, zinc turbidity, serum bilirubin, serum albumin and globulin, alkaline phosphatase, total cholesterol, per cent cholesterol esters, cephalin cholesterol flocculation and intravenous hippuric acid. An oral glucose tolerance test showed a diabetic curve, with a fasting blood sugar of 128 mg. per 100 cc. and a peak of 196 mg. per 100 cc., which was reached at one hour. An elec-

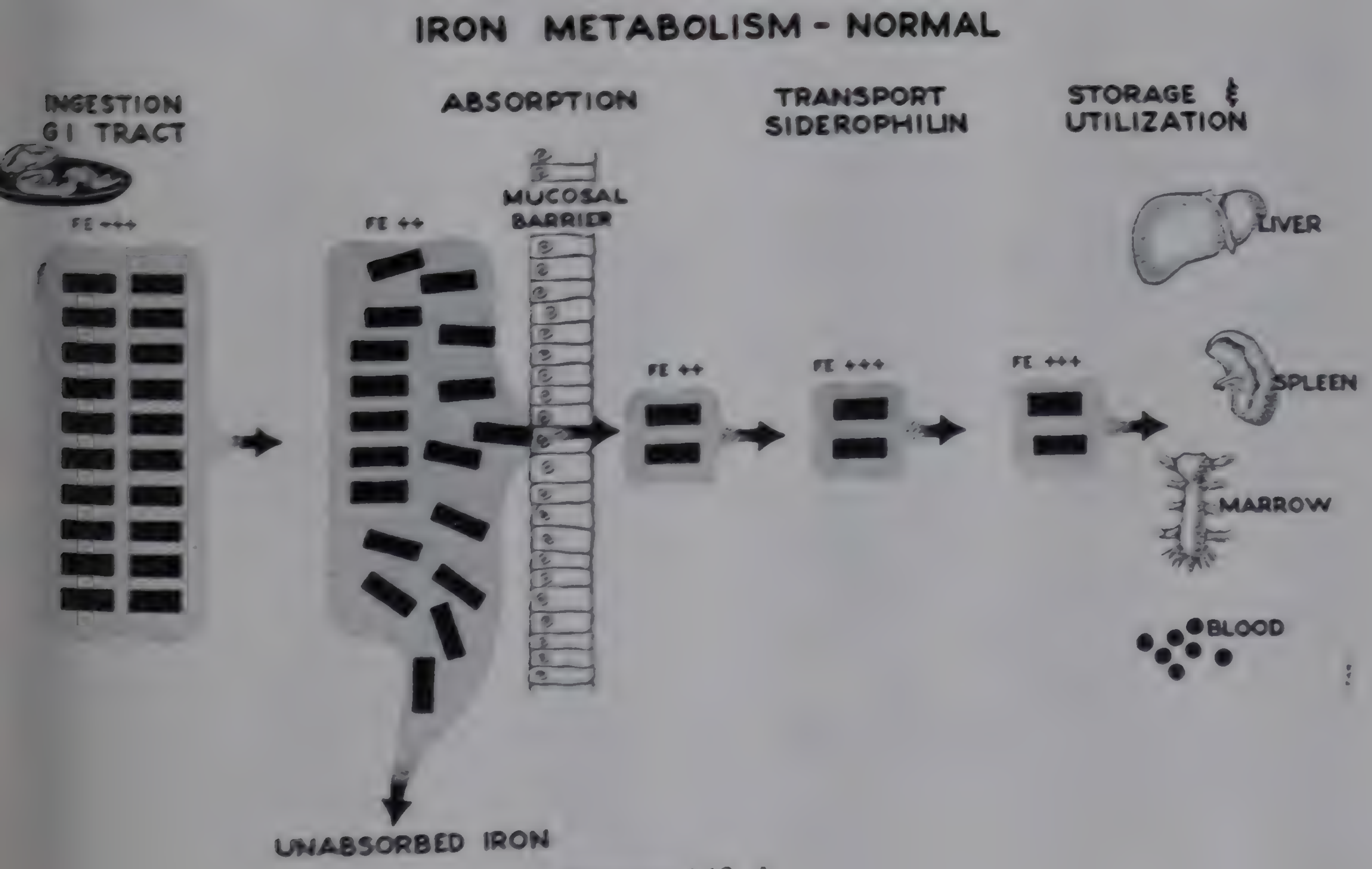


FIGURE 143 A

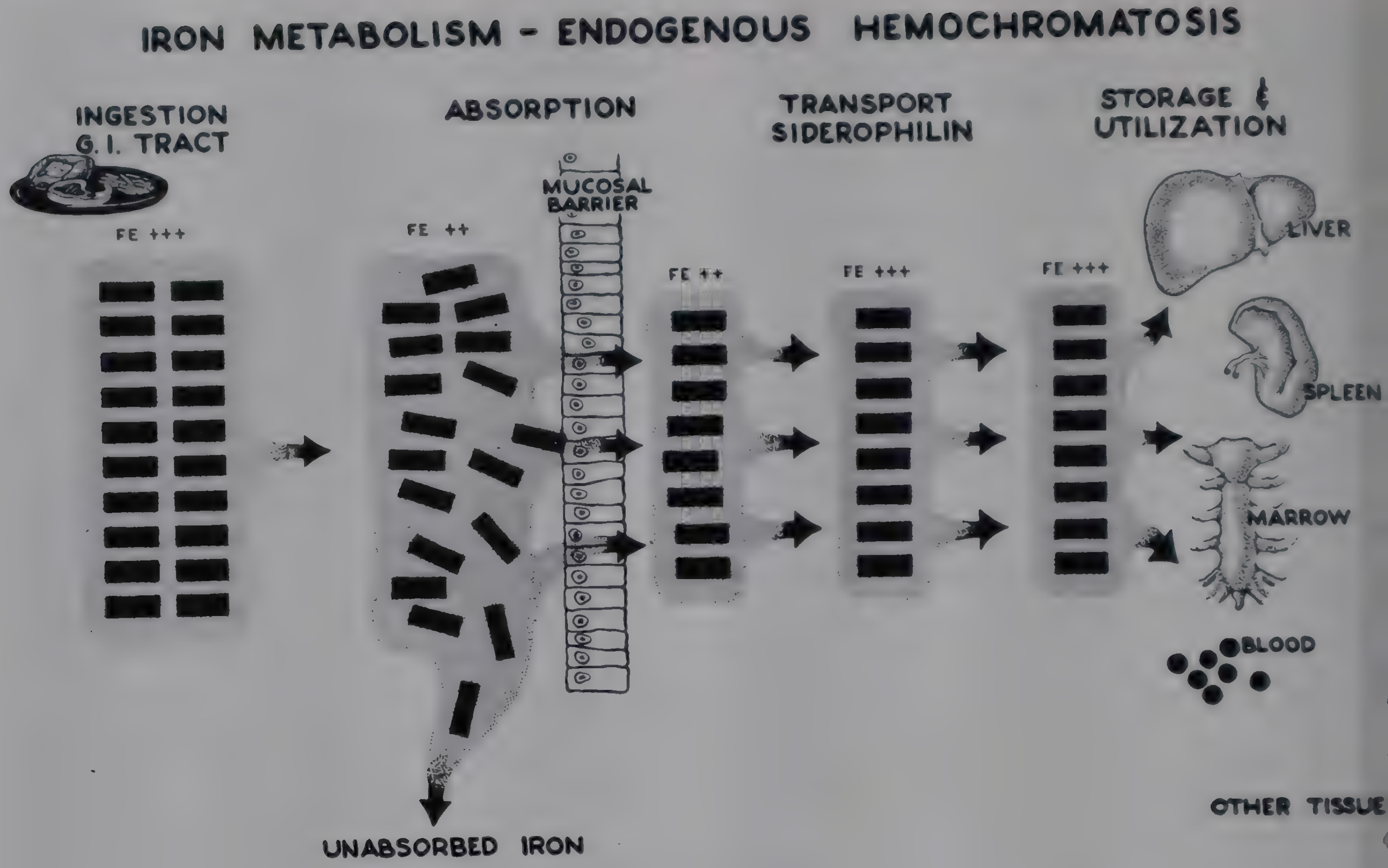

IRON METABOLISM - ENDOGENOUS HEMOCHROMATOSIS
INGESTION G.I. TRACT
ABSORPTION
TRANSPORT SIDEROPHILIN
STORAGE & UTILIZATION
MUCOSAL BARRIER
FE +++
FE ++
FE ++
FE +++
FE +++
LIVER
SPLEEN
MARROW
BLOOD
OTHER TISSUE
UNABSORBED IRON

FIGURE 143 B

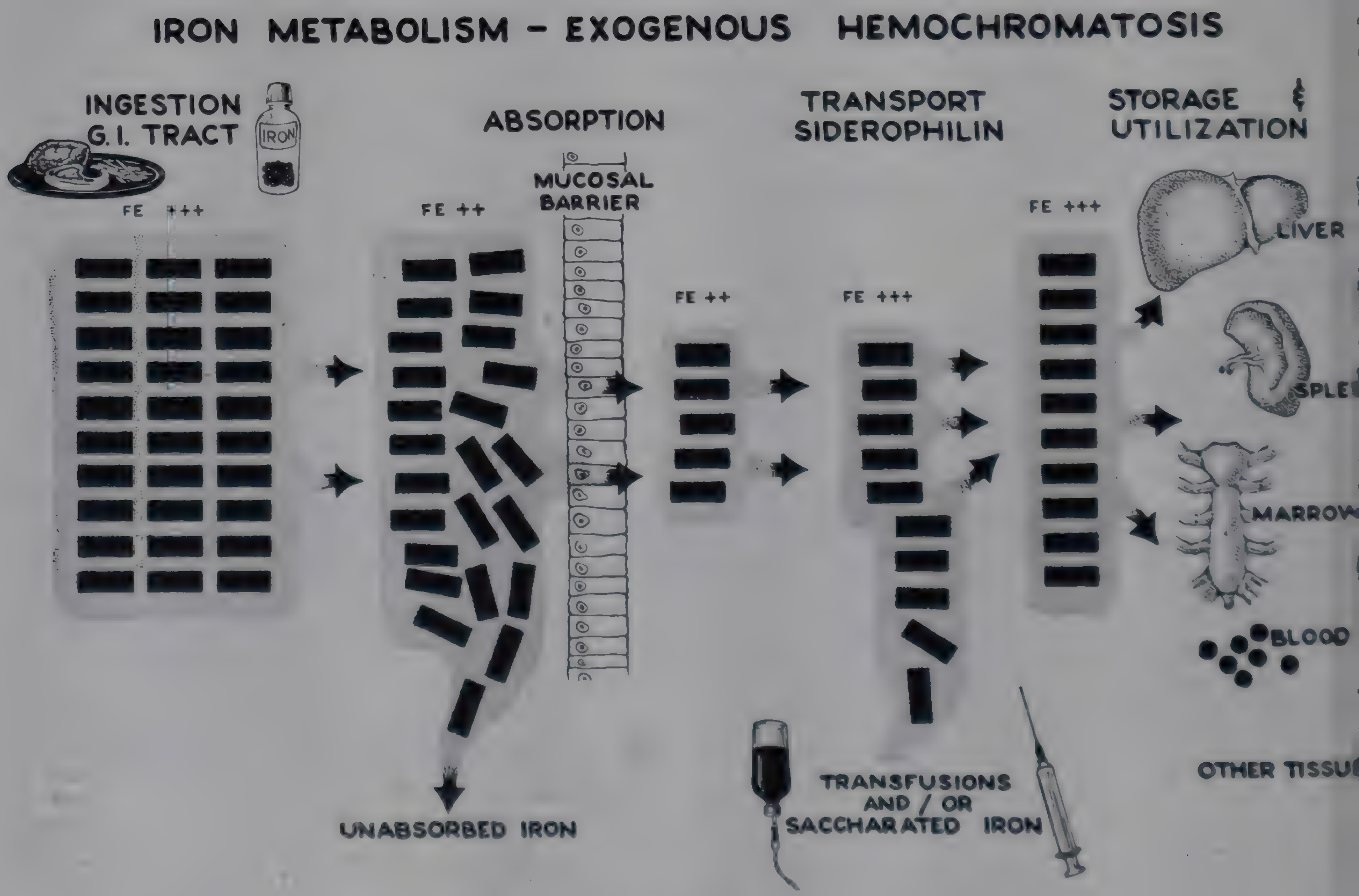

IRON METABOLISM - EXOGENOUS HEMOCHROMATOSIS
INGESTION G.I. TRACT
IRON
ABSORPTION
TRANSPORT SIDEROPHILIN
STORAGE & UTILIZATION
MUCOSAL BARRIER
FE +++
FE ++
FE ++
FE +++
FE +++
LIVER
SPLE
MARROW
BLOOD
OTHER TISSU
UNABSORBED IRON
TRANSFUSIONS AND / OR SACCHARATED IRON

FIGURE 143 C

trocardiogram showed borderline ST and T wave changes. A skin biopsy was negative for hemosiderin. A liver biopsy demonstrated marked portal and periportal fibrosis with bile duct proliferation. Portal areas were filled with macrophages containing large amounts of iron. A gastro-intestinal x-ray study was negative for esophageal varices. Further clarifying studies of the basic hematologic disease demonstrated a factor of hypersplenism. Splenectomy resulted in maintenance of a stable hemoglobin level.

The difference between hemochromatosis and hemosiderosis is the amount of iron introduced, the length of the period of accumulation and the presence or the absence of clinical disease. In endogenous hemochromatosis the mucosa of the gut absorbs excessive amounts of iron from food, and this is the sole source of the abnormal accumulation of iron in the body (Fig. 143 B). Hemosiderosis also results when iron is administered by transfusion in the form of red blood cells to patients with refractory anemias. In addition, there is also an increased absorption of iron through the gastro-intestinal mucosa, both from food and from medicinal iron preparations (Fig. 143 C). In both instances the presence of an excess of iron leads to deposits of hemosiderin in various organs and, if operative long enough, to the clinical picture of hemochromatosis. It is recognized that in cases of refractory anemia where energetic treatment is used, iron may accumulate over a shorter period than in cases of endogenous hemochromatosis. This point of view emphasizes that the differences between hemosiderosis and hemochromatosis are quantitative and chronologic rather than qualitative.[5, 6] Thus, the two terms are meaningless unless hemosiderosis is used to indicate iron-deposition-without-clinical-disease, and hemochromatosis to indicate iron-deposition-with-clinical-disease. According to this concept the term "pigment cirrhosis" would denote a relatively early stage of hemochromatosis with little or no deposition of hemosiderin outside the liver. Some investigators have attached significance to the fact that hemofuscin is present in hemochromatosis and absent in hemosiderosis.[25] This also is probably not a fundamental distinction, since the formation of hemofuscin may be explained by the longer duration of disturbed pigment metabolism in endogenous hemochromatosis.

Certain structures in the body, when infiltrated with iron, undergo fibrosis and suffer a marked disturbance of function (e.g., pancreatic islets), whereas others show no anatomic or functional abnormalities (e.g., chief cells of the gastric mucosa).[4] It is possible that the former structures are more susceptible than the latter to the presence of iron and that therefore their architecture and metabolism are interfered with more readily. The duration of involvement of various organs also may be of importance. Certain organs, such as the liver and the pancreas, which store iron readily, become involved at a much earlier stage of the disease, and for this reason show structural and functional changes at a time when other organs which store iron less readily show no such changes. Little correlation has been observed between the amounts of iron present and the degree of anatomic and functional changes in a given organ.

The fact that hemochromatosis is so rare in females, particularly during the childbearing age, gave rise to the concept that loss of iron through menstrual bleeding can prevent clinical manifestations of the disease. It has been estimated that during the reproductive life of a woman 15 Gm. of iron are lost in this manner. In addition, each childbirth accounts for a further loss of approximately 500 mg. of iron.[23] Consistent with this concept is the observation that hemochromatosis occurs only in middle-aged women or in women who have disturbances associated with a grossly diminished menstrual flow and are usually childless.[4, 29]

PATHOLOGY

In hemochromatosis practically all tissues of the body show the characteristic deposits of hemosiderin, although certain tissues are involved more extensively than others. Of special importance in this disease are the abnormalities of the skin, the liver, the pancreas, the heart, the stomach and the endocrine organs.

SKIN

Grossly, the skin appears thin and dry, with a notable sparseness of hair. Microscopic study shows atrophy of the epidermis, the hair follicles and the sebaceous glands. Sometimes the epidermis is reduced to a sheet only 4 or 5 cells deep; the interpapillary processes are flattened. Areas of pigmentation show a marked increase in melanin, particularly in the basal layers of the epidermis. Hemosiderin, if present, occurs as small granules diffusely distributed through the corium and about the acini of the sweat glands. Occasional clumps of hemofuscin, a sulfur-containing iron-free pigment, are found just under the epidermis and sometimes in the walls of blood vessels. It is believed that the deposits of hemosiderin in the skin are too scanty to show any detectable color and that the increase of melanin is responsible for the brown pigmentation. The "slatey" bluish-gray appearance of certain areas is thought to be produced by viewing an increased amount of melanin through a greatly reduced number of superficial epidermal cells.[4]

LIVER

Sheldon[47] stated that the liver in hemochromatosis is usually greatly enlarged and weighs an average of 2,361 Gm. At autopsy the liver is reddish brown and has a hobnail appearance. It is firm in consistency and feels gritty on sectioning. Microscopic examination reveals two outstanding features: extensive pigmentation and pronounced fibrosis. Two types of pigment are present: hemosiderin and hemofuscin. In the hepatic cells the hemosiderin appears as fine, dustlike particles, either scattered or in clumps. Eventually, these conglomerates fill up the entire cell and apparently destroy it. Although it is often difficult to determine what portion of the lobule is involved most, the periphery appears to contain the most hemosiderin. Hemosiderin is also found in the broad bands of fibrous tissue usually present, in the connective tissue cells and in the extracellular areas. The Kupffer cells are distended with hemosiderin and are easily recognized. Hemosiderin is found also in the capillaries of the liver capsule and in the cells of the bil ducts. Hemofuscin is present in much smalle amounts in the walls of the large arteries an veins in the liver capsule, in the connecti tissue and, to a lesser extent, in the hepat polygonal cells.

In addition to the enormous amounts (hemosiderin, the liver shows the structur alterations of portal cirrhosis, with varyi amounts of intralobular fibrosis. Indeed, patients treated by repeated phleboton which succeeded in removing virtually iron deposits from the liver, serial liver b opsies have shown a picture indistinguishab from that seen in simple portal cirrhosis. Furthermore, no lessening of fibrosis was a parent after venesections.

PANCREAS

The pancreas may or may not be enlarge In most cases it is deeply pigmented and e hibits a reddish-brown color similar to th of the liver; it is more firm in consisten than the normal pancreas.

Microscopic examination of the pancrea tissue shows heavy deposits of hemosider especially in the acinar cells and in the isl of Langerhans. According to Sheldon,[47] t islets of Langerhans are pigmented w hemosiderin in about 80 per cent of cas The degree of pigmentation of the islets h no consistent relation to the degree of d betes mellitus. In most of the reported ca the number of islets of Langerhans was minished, and in some they could not be id tified. Hemofuscin granules also can be tected in the pancreatic tissue. Other patl logic changes consist of fibrosis and a mark relative increase in the number of aci cells, many of which show degenerat changes. At times a fatty metamorphosis evident.

HEART

Upon gross examination the heart is of deep brown in color. Hemosiderin has b found in the heart muscle fibers in nearly cases of hemochromatosis. Characteristica the hemosiderin is arranged at the poles the nuclei. These deposits have resulte degenerative changes in a few instances rarely cause fibrosis.

STOMACH

In rare cases of hemochromatosis the gas- c mucosa may show a brown pigmentation the naked eye. Considerable amounts of mosiderin were found in the chief cells of e gastric mucosa in 11 cases studied with opsy by Althausen and co-workers[4] (Plate . A rough correlation existed between the tensity of pigmentation in the liver and in e gastric mucosa. A gastric analysis after stamine revealed normal values for hydro- loric acid and normal or slightly low values r pepsin in 9 patients in whom the gastric ucosa, apart from the deposits of hemo- lerin, appeared normal histologically. hese findings indicate that the presence of mosiderin in the chief cells, even in large nounts, had little or no effect on their se- etory activity. In 2 cases in which some rophy of the chief and the parietal cells was oted, the secretion of hydrochloric acid and pepsin was lowered. The atrophy probably as not due to the presence of iron, since the rietal cells of the gastric glands, which ntained little or no iron, were atrophied to e same degree as the chief cells, which con- ined large amounts of iron.

ENDOCRINE GLANDS

Hemosiderin deposits are found in the pi- itary, the adrenals, the testes, the thyroid d the parathyroid glands.[47] These are of terest in view of the endocrinopathies hich may be present in patients with hemo- romatosis. No specific abnormalities of yroid or parathyroid function have been ported. On the other hand, clinical mani- stations of "feminization," such as hypo- asia of the male genitalia and sparsity of ody hair, are frequent. The testes may be rophic but usually contain little hemosid- in. These changes have not been correlated ith morphologic changes in the pituitary or e adrenals, and no other acceptable expla- ation has been advanced.[3] Melanin pigmen- tion and physical weakness so often found hemochromatosis have been ascribed to lrenal insufficiency. However, this relation- ip never has been clearly demonstrated. wo of our cases were first misdiagnosed as ddison's disease; in these patients blood ectrolytes and blood pressure were normal. The latter was normal or high in all but one of the remaining 21 cases in this series.[4]

DIAGNOSIS

The principal physiologic abnormality in hemochromatosis is increase in storage iron, regardless of its source. It is now believed that if sufficient iron is present in the tissues over long enough periods of time, changes will take place leading to the classic manifestations of this disease, namely, hepatic cirrhosis, diabetes mellitus and skin pigmentation.[5] The diagnosis of hemochromatosis depends, therefore, upon the demonstration of increased stores of iron, plus an empiric delineation of certain additional clinical features. Thus, the term "hemosiderosis" or "prehemochromatosis" might be used to signify increased amounts of tissue iron alone, and the term "hemochromatosis" to indicate a characteristic combination of abnormal accumulations of iron, plus clinical evidence pointing to involvement of the liver, the pancreas and the skin.

The diagnosis of hemochromatosis should be considered by the examining physician in all patients with increased pigmentation of the skin who evidence symptoms of weakness, fatigability and liver enlargement or pain. Polyphagia, polyuria, polydipsia and other symptoms of diabetes in a pigmented patient likewise should direct the attention of the physician to the possibility of hemochromatosis, as should the combination of diabetes mellitus and hepatic cirrhosis, even in the absence of increased pigmentation of the skin. Diabetes and evidence of hepatic disease in a pigmented patient justify a tentative diagnosis of hemochromatosis, subject to confirmation by laboratory procedures. When suspicion is aroused, other abnormalities commonly encountered in the history and the physical examination of patients with hemochromatosis should be looked for, particularly in regard to the texture of the skin, distribution of hair, the condition of the testicles in the male and the menstrual history in the female.

The results of liver and pancreatic function tests may be entirely within normal limits in this disease; on the other hand,

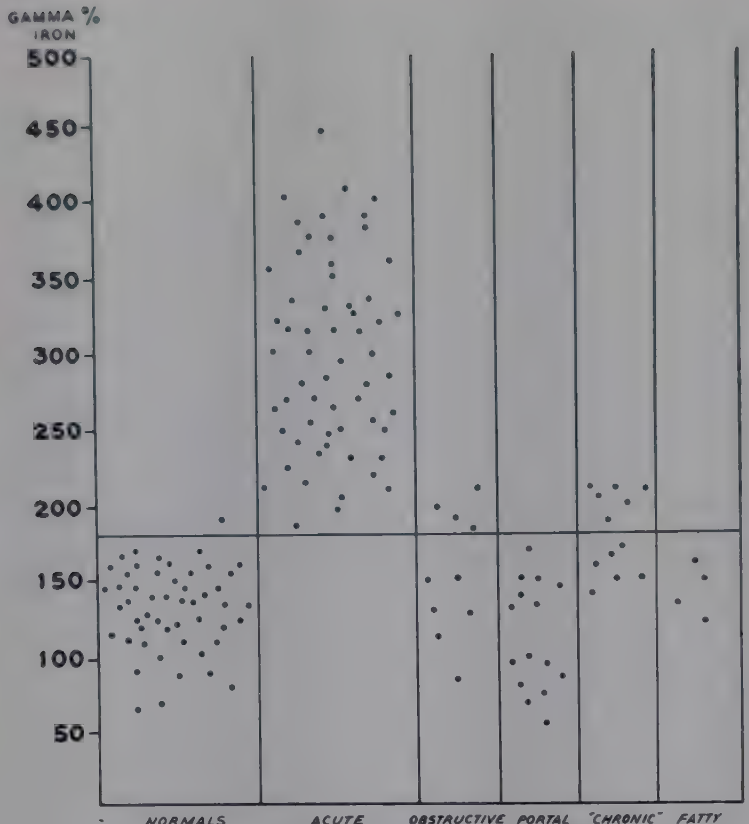


FIG. 144. Serum iron levels compared in normal subjects and in patients with various liver and biliary tract diseases. (Peterson, R. E.: J. Lab. & Clin. Med. 39:225-236)

demonstration of abnormal liver and pancreatic function does not constitute absolute proof that hemochromatosis is present. However, the finding of a "diabetic" glucose tolerance curve or of impaired liver function in suspected cases, will greatly strengthen other evidence.

The most useful diagnostic tests are based on demonstration of abnormal iron metabolism. The laboratory findings of elevated serum iron and decreased iron-binding capacity of the serum are strongly suggestive in establishing the diagnosis; they are not decisive, however, since relatives of patients with hemochromatosis may exhibit similar abnormalities without showing other overt evidence of the disease.[37] Markedly elevated serum iron levels also may be found in patients with hepatitis or chirrhosis of the liver due to other causes, although the extremely high levels which may occur in hemochromatosis have not been described in patients with chronic liver disease[40] (Fig. 144).

The sine qua non in this disease is the demonstration of abnormal amounts of iron in the tissues. The presence of hemosideri granules in epithelial cells desquamated int the urine is strongly suggestive of the diag nosis;[44] however, since only a minority o patients with hemochromatosis show thi finding, the disease cannot be ruled out b its absence.

Biopsies of certain tissues have been foun useful in the diagnosis of this disease.

SKIN

If positive, the skin biopsy can be used t clinch a diagnosis of hemochromatosis, pro vided that local sources of hemosiderin, suc as varicose veins and "vagabond's disease, can be excluded.[4] If it is negative, on th other hand, the disease cannot be ruled ou In 13 cases of hemochromatosis with pig mentation in which a biopsy was done, onl 7 were found to have detectable amounts hemosiderin in the skin by Althausen.[4] Blu discoloration of the skin following intr dermal injection of acidified potassium fe rocyanide (Fishback test[17]) has been pr posed as a diagnostic aid in hemochrom tosis. However, this test has been found t be even less reliable than the presence hemosiderin in the cells of the urinary sed ment or in the skin.

STOMACH

In Althausen's experience,[4] gastric biop showed considerable deposits of hemosider in the chief cells of the gastric glands in a of 11 patients subjected to this procedur These results suggest that gastric biopsy is far more reliable means of diagnosis in hem chromatosis than biopsy of the skin. Sin this observation has been confirmed by son investigators[34] but not by others,[45] more e tensive studies are needed before gastr biopsy can be evaluated as a means diagnosis.

LIVER

Of all present measures for the diagno of hemochromatosis, liver biopsy has prov to be the most satisfactory.[14, 32, 51] Since t liver is the main storehouse for iron in t body, the absence of increased amounts iron in this organ will rule out this disea decisively. By the same token the presence increased amounts of iron in the liver, even if the other characteristic findings of hemochromatosis are lacking, probably means that the disease is in an early stage, provided that other forms of siderosis caused by repeated blood transfusions, administration of iron or nutritional imbalance can be ruled out. Admittedly, as pointed out by Davis,[14] liver biopsy is less satisfactory in patients with hemochromatosis than in patients with other hepatic diseases, since there is more pain and less certainty of obtaining an adequate specimen. Despite certain dangers attendant to its use, even with proper precautions, the liver biopsy stands *alone* in its value in the diagnosis of hemochromatosis and should be used in all suspected cases, provided that no contraindications are present.

Two new, and as yet little tried, procedures have been proposed: (1) Examination of the aspirated sternal marrow for increased amounts of hemosiderin is a highly accurate means of diagnosis, according to Rath and Finch,[42] who stated that hemochromatosis can be positively excluded when increased amounts of hemosiderin are *not* demonstrated. The examination of many cases of hemochromatosis by this method will be necessary before such a conclusion can be substantiated. (2) Sosman and his associates have called attention to the diagnostic use of x-ray examination of the liver.[37] They demonstrated an increase in liver density and a double contour line along the diaphragmatic border in 9 of 10 patients with hemochromatosis studied by means of x-ray films of the abdomen. Although other investigators[48] have searched for this sign, it has not been found with any consistency to date, and the use of this method in the diagnosis of hemochromatosis also must await confirmation.

TREATMENT

Treatment of the patient with hemochromatosis is concerned with the organs directly involved in the disease, such as the liver, the pancreas and the heart, and with the specific anomalies of excessive absorption and deposition of iron.

Heart failure and cardiac arrhythmias should be managed in the usual way with the use of digitalis, quinidine, diuretics and restriction of salt intake. However, the long-term success of such a regimen usually has been slight, particularly in the control of arrhythmias, and the outlook for such patients as a whole is poor. On the other hand, the prognosis in coexistent heart disease unrelated to the hemochromatosis is more favorable.

With the use of insulin, the management of the associated diabetes mellitus has presented no particular problem except under unusual circumstances. Both insulin-hypersensitive and insulin-resistant types of diabetes occur in hemochromatosis. The patient with this condition should be given a diet adequate in protein, calories and vitamins. This is particularly important because of the coexistence of hepatic disease. Sufficient insulin should be used to prevent hyperglycemia and glycosuria. Usually, no medication is required as a substitute for digestive enzymes of the pancreas in hemochromatosis. As a remedy for indigestion or to improve nutrition, pancreatic extracts may be tried, especially in cases where a known deficiency of enzyme secretion by the pancreas exists.

The therapy of the associated liver disease is mainly dietary; large amounts of protein and carbohydrate, moderate amounts of fat and abstinence from alcohol should be prescribed. Where liver function is stable, as is usually the case, activity may be advised as tolerated. However, the activities of the patient should be restricted whenever deterioration or improvement in hepatic function is observed.

On occasion testosterone, given parenterally in moderate doses, has been successful in improving nitrogen balance and the general well-being of these patients.

With the use of measures directed toward control of the diabetes and improvement of liver function, some, but not striking, progress has been made in the management of patients with hemochromatosis. In many instances this type of treatment results in temporary improvement; in the usual case, however, despite the patient's strict adherence to this regimen, the disease continues its slow but persistent progression.

A new and promising development in the treatment of hemochromatosis, which has been used recently and publicized by Davis and Arrowsmith and others,[8, 13, 14, 29] involves removal of iron from the body by frequently repeated phlebotomies. Davis and Arrowsmith, in a recent summary of the experience with phlebotomy in 15 cases of hemochromatosis, 6 of which were observed by them personally, reported a satisfactory response to this treatment in 12.[14]

The procedure consists first in removing 500 cc. of blood from the patient daily until the hemoglobin reaches a level of 10.5 to 11.5 Gm. per cent and the hematocrit is approximately 35 per cent. The authors advocate separation of the plasma from the red blood cells and its return to the patient at the time of the next phlebotomy. In the experience of other clinicians return of the plasma has not been found to be necessary. When the hemoglobin and the hematocrit have dropped sufficiently, venesection is carried out every 4 to 8 days as needed to maintain the blood at the stated lower levels. The authors pointed out that in their experience patients with hemochromatosis tolerate frequent bleedings remarkably well. In some of their patients the blood regenerated at the rate of 2,000 to 2,500 cc. every 3 weeks. One patient is described from whom 19,000 cc. of blood were removed in 17 weeks, and another from whom a total of 96,400 cc. of blood was taken in less than 4 years (Table 41). In 4 patients from the same series, the amount of iron removed from the tissues by venesection over periods of 4 to 6 years was calculated to be from 20 to 50 Gm.

Table 41. The Quantities of Blood and Iron Removed by Repeated Phlebotomies from 5 Patients with Hemochromatosis

Patient	Bleeding (liters)	Time (months)	Iron (Gm.)
P. S.	40	22	20
A. W.	40	16	20
G. P.	51	21	26
R. B.	8	4	?
B. M. U.	103	54	52

Modified from Davis, W. D., Jr., and Arrowsmith, W. R.: Ann. Int. Med. **39**:723-734, 1952.

Since earlier efforts to restrict the ingestion of food iron have met with little success, Davis and Arrowsmith also advise an attempt to decrease absorption of iron by administration of aluminum hydroxide gel.[14] Thi
raises the pH of the duodenal contents an
tends to maintain the ingested iron in th
ferric form, which is absorbed less readil
from the intestine than the ferrous form. I
order to keep the absorption of iron at
minimum, it is also advisable to provide
diet with a high phosphate content. This
possible if much of the protein in the die
consists of meat. If cirrhosis of the liver an
diabetes are present, this program is supple
mented by the usual measures indicated fo
these conditions.

Improvement in the patient's well-bein
strength and ability to work usually occurre
a few weeks after the program of venesectio
was initiated. Diminution of the size and th
tenderness of the liver and improvement
hepatic function and diabetic status we
noted in a large proportion of these patient
In all reported cases the patient's complexio
lightened noticeably. In one patient electr
cardiographic abnormalities were lessen
after repeated phlebotomies.

In their summary of the results of phl
botomy, Davis and Arrowsmith reported th
serial liver biopsies showed a remarkable r
duction in hemosiderin deposits in the liv
of patients studied by this procedure; ho
ever, no decrease in the amount of scar ti
sue was noted.

A single patient studied by one of
(V.M.S.) illustrates the improvement whi
can result from repeated phlebotomies.

A 50-year-old army officer gave a histo
of fatigue and anorexia, which had develop
gradually over an 8-month period. O
month after these symptoms first occurre
he noted moderate jaundice and dark uri
which lasted for 3 months and then gradua
diminished. At the time of admission to t
hospital he complained of fatigue, weakne
anorexia, abdominal distention, and a gra
ual loss of 15 pounds in weight. The patie
used only small amounts of alcohol and h
been exposed to no other hepatotoxic m
terials.

Physical examination showed a norma
developed and nourished man with no e
dence of pigmentation in the skin or the m
cous membranes. The patient exhibited
sparsity of body hair. Palmar erythema a
a few spider nevi over the face, the ne
and the shoulders were noted. The liver w

enlarged to 7 cm. below the right costal margin and was very tender on palpation and percussion. The spleen was not palpable. A small amount of ascites was found. The penis was normal, but the testes were soft. The hemoglobin, the red and the white blood cell and differential counts were normal; results of tests for serum bilirubin, alkaline phosphatase, serum proteins and thymol turbidity were all within normal limits. Bromsulphalein retention was 20 per cent in 45 minutes (5 mg. per kilo). The serum iron was 275 µg. per cent, and the serum iron-binding capacity was fully saturated. The glucose-tolerance test showed a diabetic curve, although a number of urine specimens were negative for sugar. Hemosiderin could not be demonstrated in the urine. A biopsy of the skin and of the gastric mucosa showed no hemosiderin deposition. A sternal bone marrow aspiration was strongly positive for hemosiderin. A liver biopsy specimen taken prior to treatment is illustrated in Plate 1. Treatment consisting of bed rest and a high-protein, high-caloric diet with multiple vitamin supplements was only partially successful; the patient continued to complain of fatigue and lack of initiative, but to a lesser degree than previously.

Six months after admission a program of frequent phlebotomies was begun. At the same time the patient was given added dietary phosphate to help lessen absorption of ngested iron. At this time the red blood count was 5.3 million cells, hemoglobin 15 Gm., and hematocrit 45 per cent. The liver was 14 cm. and the spleen 2 cm. below the costal margin. During the next 10-month period, 24,000 cc. of blood was removed by means of 39 phlebotomies. At the end of this time the red blood count was 4.1 million cells, hemoglobin 13.2 Gm., hematocrit 44 per cent, and reticulocyte count 4.5 per cent. Bromsulphalein retention was lowered to 5 per cent; results of other liver function tests remained normal. The serum iron measured 220 µg. per cent. During the next 4 months t became necessary to reduce the phlebotomies to one every 2 to 4 weeks.

After 14 months of therapy a total of 37,000 cc. of blood had been removed, which accounted for approximately 15 Gm. of iron. At this time the red blood count was 3.0 million cells, hemoglobin 8.5 Gm., and hematocrit 34 per cent; the serum iron was 40 µg. per cent. Examination of the sternal marrow revealed changes consistent with iron deficiency anemia. A liver biopsy specimen obtained at this time is illustrated in Plate 3. A glucose-tolerance test showed some improvement but was still abnormal. Since the beginning of treatment with phlebotomy, the patient had been able to tolerate more physical activity, and his sense of well-being had increased. In spite of slight anemia the patient complained of a fullness in the head and dizziness, which heretofore had always been relieved by venesection. However, results of a blood-volume determination were within normal limits. Enlargement and tenderness of the liver persisted, but the spleen was no longer palpable. During the following 12 months it was necessary to bleed the patient on 6 more occasions to maintain a moderate anemia and to perpetuate the marked clinical improvement.

It is necessary to point out that not all patients suffering from hemochromatosis can be treated by phlebotomy. Some patients do not show a sufficiently good hematopoietic response to the loss of blood to permit further bleeding.[24] Some patients already are anemic when they come under observation, and others may be in too poor a condition because of the liver disease or other complications to permit treatment by repeated venesection.

A novel approach to removal of iron from the body of patients with hemochromatosis recently suggested by Wishinsky and coworkers[55] consists in the mobilization of iron by intravenous injections of ethylenediaminetetraacetic acid. In an iron balance study of a single patient with hemochromatosis, increased amounts of iron were excreted in the urine following the injection of this acid. Unfortunately, the quantities of iron removed in this manner were far too small to be of practical aid in the management of patients with hemochromatosis. However, this method does point the way for biochemical means of treatment of this disease.

PROGNOSIS

In the past the survival of patients after the diagnosis of hemochromatosis varied within wide limits. For example, in Butt and Wilder's series[12] the duration of life varied from 1 month to 13 years, with an average survival of 1½ years after diagnosis. The use of insulin and general measures of liver therapy has gradually bettered the outlook for such patients. Despite this treatment, however, the disease usually progresses steadily, and death ultimately results from intercurrent infection, hepatic coma, rupture of esophageal varices, heart failure or the complications of diabetes. The use of repeated phlebotomies in therapy should produce further improvement in the prognosis and possibly arrest the progress of the disease.

Another factor may also influence favorably the prognosis in hemochromatosis in the future. Although it occurs in about 0.1 per cent of the general population,[2] primary carcinoma of the liver has been especially frequent in patients with hemochromatosis. Berk and Lieber[7] in 1941 pointed out that carcinoma of the liver is present in 7.3 per cent of patients with hemochromatosis, in contrast with an incidence of only 4.5 per cent in patients with other types of cirrhosis of the liver. Warren and Drake[54] found that whereas carcinoma of the liver developed in approximately the same percentage of their patients with cirrhosis of the liver, 18.9 per cent of their patients with hemochromatosis died from this cause. Therefore, it would seem that beyond the carcinogenic tendency already present in cirrhosis of the liver, additional factors which favor the production of carcinoma are brought into play through presence of increased amounts of iron in t organ. Theoretically, then, removal of i from the liver should effect a diminution the incidence of primary carcinoma of organ in patients with hemochromatosis.

A true perspective for hemochromatosi just beginning to emerge. The interest the curiosity shown through the years h proved to be fruitful in elucidating many the mysteries of this disease. However, spite the great progress made to date m questions remain. Future follow-up stu of groups of patients, such as the series ported by Davis and Arrowsmith, who h been treated by repeated venesections sho provide data on the ultimate outcome of diabetes and the hepatic cirrhosis and on incidence of carcinoma in hemochromat

Among other goals which await fu achievement are: (1) a clarification of physiologic defect present in endogen hemochromatosis leading to uncontrolled sorption of massive amounts of iron; (2) exact role of the stored iron in the produc of tissue pigmentation and fibrosis; (3) effective method of eliminating iron from body without the constant strain on the h atopoietic organs imposed by repeated p botomies; and (4) an efficient way of bl ing excessive absorption of iron from intestine without interfering with the no absorption of foodstuffs and minerals c than iron.

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hapter 18

HEPATO-LENTICULAR DEGENERATION

W. B. Matthews, D.M.

Hepatolenticular degeneration is a disease childhood and early adult life in which rrhosis of the liver is associated with cere- al lesions, predominantly in the basal gan- ia. This remarkable combination was first tablished as a specific clinical entity by ilson[48] who, in a monumental paper, col- cted earlier reports and minutely described e condition under the title of "progressive nticular degeneration." Hall[20] recognized e essentially similar nature of many cases scribed under the unsatisfactory title of pseudosclerosis"[42, 47] and also the impor- nce of the characteristic corneal pigmenta- on as a diagnostic sign. He preferred ilson's alternative name of "hepato-lenticu- r degeneration," and since then this has een universally adopted, with "Wilson's dis- ase" as an acceptable abbreviation. Little as been added to these masterly clinical de- riptions, but the disease, offering as it does gap in the hitherto impenetrable obscurity the degenerative diseases of the nervous stem, has engaged the attention of many vestigators. Recent years have revealed impses of a complex underlying metabolic isorder, and in the following account of the isease this aspect will be emphasized.

INCIDENCE

Hepato-lenticular degeneration is uncom- on but not excessively rare; well over 200 ases have been described in the literature. oth sexes are affected, with an apparent ight preponderance in males. The onset of mptoms is usually between the ages of 10 nd 25 and only very exceptionally after the e of 40.

The familial nature of the disease has been cognized from the first, and it is very probable that this is due to transmission by recessive inheritance and not to exposure of members of a family to a common noxious environment. Statistical evidence of such inheritance is difficult to procure, as the figures are heavily weighted by the natural tendency to full reporting of families in which many members are affected, while the number and the ages of sibs of apparently sporadic cases are frequently omitted.[33] Consanguinity of parents is unduly frequent,[2] and at least 5 pairs of identical twins with the disease have been reported, and no instance is known in which only one of an identical pair has been affected. Bearn[4] was able to avoid the fallacies inherent in collecting cases from the literature by analyzing an unusually large personal series. The ratio of affected to unaffected sibs was close to that expected from a recessive autosomal inheritance.

CLINICAL FEATURES

The occurrence of symptoms of hepatic and cerebral disease varies greatly from case to case. In rare instances the whole course of the disease may be that of hepatic cirrhosis with recurrent jaundice, ascites, hematemesis and other hemorrhagic manifestations and terminal hepatic coma.[28] The great majority of cases, however, present with neurologic symptoms. Inquiry may reveal unexplained episodes of jaundice or ascites in the past, and there may be a history of dyspepsia, anorexia and vague ill-health possibly attributable to hepatic disease. When present, the symptoms of cirrhosis are in no way distinctive, and no characteristic disturbance of liver function has been found. Evidence of cirrhosis usually is confined to an enlarged spleen or to some slight abnormality in liver-function tests or may be entirely absent. In some families the disease tends to be of similar type in all affected members,[3] but this is not always so. It is probable that a number of cases of "juvenile cirrhosis" are in fact examples of hepato-lenticular degeneration and that the diagnosis is not often considered in the absence of neurologic signs or of a family history.

Apart from the rare cases with entirely hepatic symptoms, the "abdominal Wilson" of certain authors, most cases fall into one of two groups: those of early onset, rapid progression and symptoms due mainly to rigidity and disorders of posture, and those of later onset, more chronic course and with tremor as the predominant symptom (pseudosclerotic type). There is no sharp dividing line; indeed, some patients may pass from one type to the other[29] but the distinction is of some practical importance.

In the first group the patient is usually a child, and the presenting symptom may be a stiffness in the gait, involuntary lapses of posture or clumsiness in skilled movements. Handwriting deteriorates, and eating becomes slovenly. Soon, speech is affected and becomes monotonous in tone or sometimes explosive. Dysphagia is a prominent and distressing symptom. Tremor frequently adds to the disability, and all movements become increasingly clumsy until the child can no longer feed himself, and walking becomes a succession of rapid jerks. Examination at this stage shows an unmistakable picture. The mouth is open in a fixed grin; speech is unintelligible or completely absent; and saliva dribbles from the mouth. The tongue is rigid and can be moved only with difficulty. The limbs adopt rigid postures, the details of which vary from case to case (Fig. 145). The rigidity can be overcome readily by passive movement in most cases and fluctuates greatly in intensity. Until the final stages the postural rigidity can be interrupted by the patient, but only for brief moments during which extremely rapid movements can be performed. Tremor is common but not invariable and consists of a rapid rhythmic movement which is greatly enhanced on attempting any sustained activity such as lifting a cup. The combination of the tremor and the fluctuating rigidity eventually leads
complete helplessness, as on every attempt
movement the limbs jerk as if on invisi
wires (Fig. 146). The intellect often remai
unimpaired but is masked by the fixed g
and the loss of speech. Occasionally, deme
tia and behavior disorders occur, and em
tional overreaction is rather common.

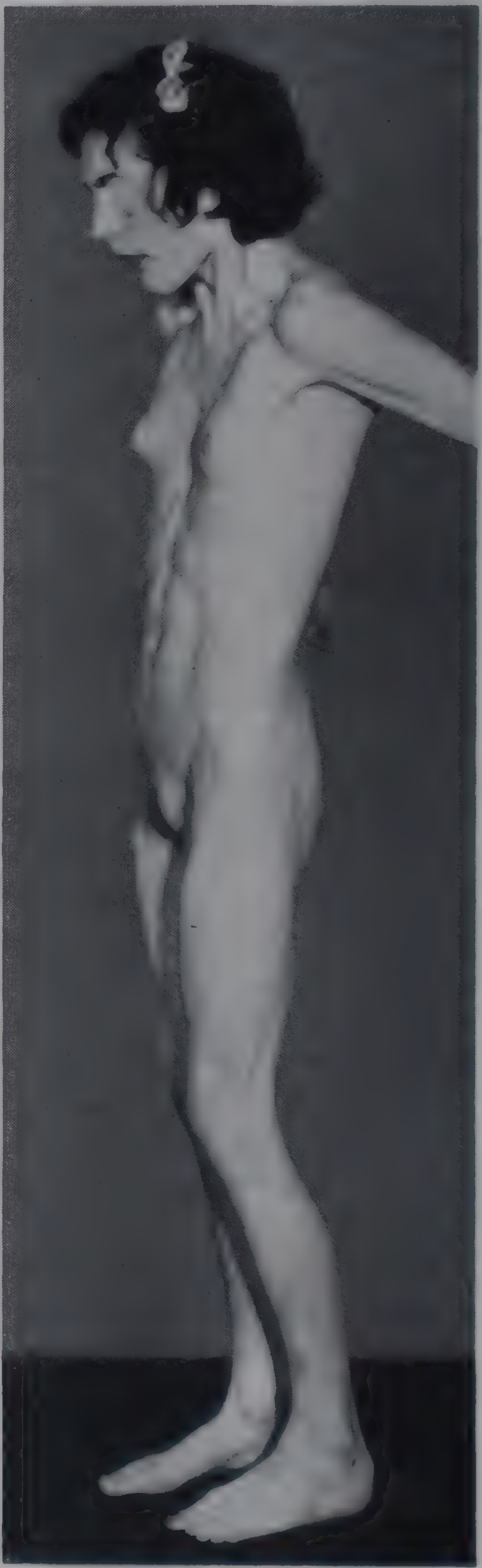

FIG. 145. Girl, aged 13, with Wilson's disease, showing the posture habitually adopted by this patient.

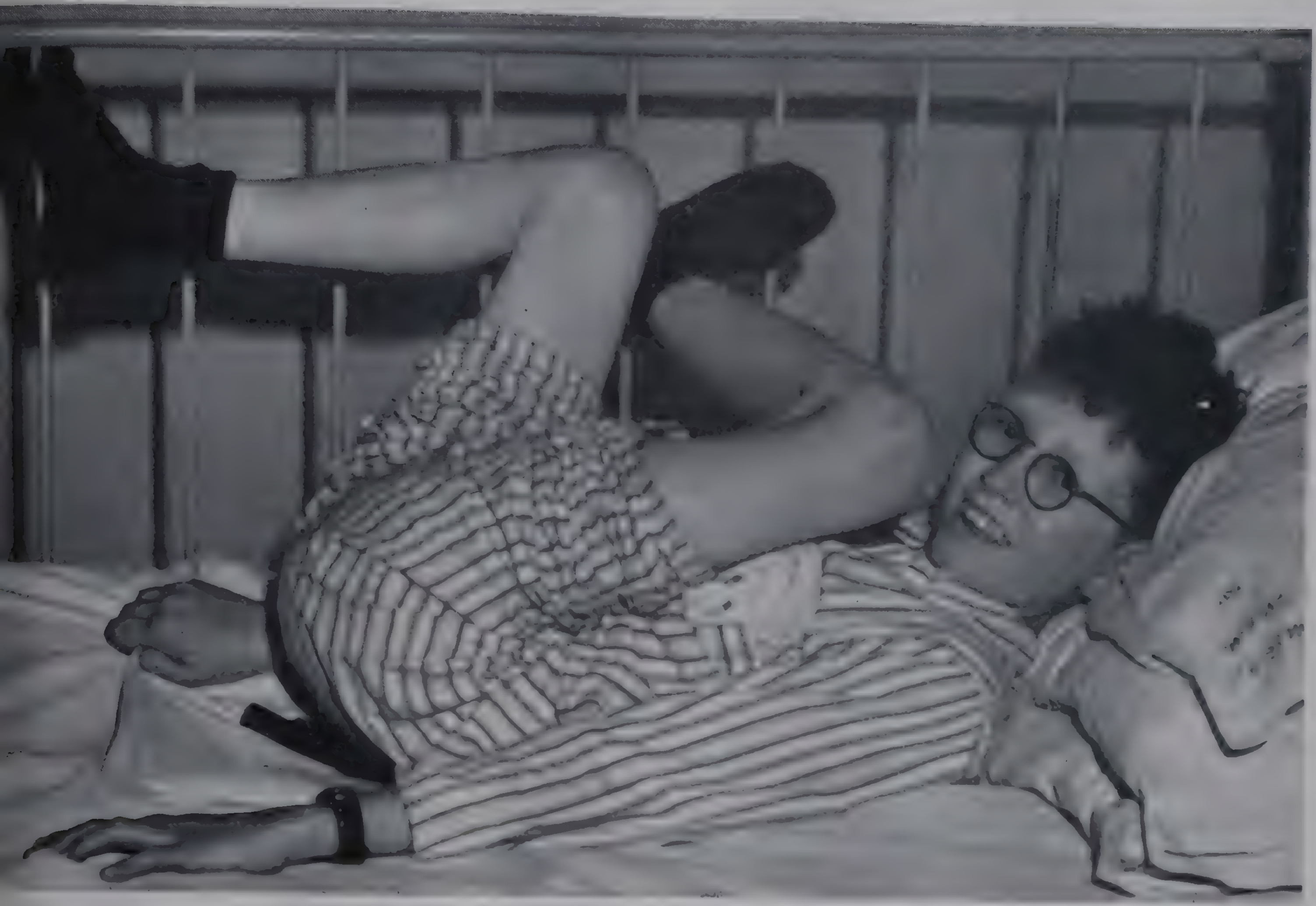

FIG. 146. Boy, aged 13, with Wilson's disease. The face is contorted in a grin, and he is attempting to control the involuntary jerking of the legs produced by raising them from the bed.

In the second group of cases tremor is the
resenting symptom and characteristically
egins in early adult life. The tremor is
oticed first on sustained movement, such as
riting, eating or driving, and may be asym-
ietrical but frequently involves all limbs and
lso the head and the jaw. Symptoms of ri-
idity, dysarthria and dysphagia may de-
elop, but tremor may be the only symptom
or a number of years. At this stage no ri-
idity may be detected, and the facial ex-
ression and the posture are normal. The
emor is usually absent at rest, but on at-
mpting any movement or sustained posture
rapid rhythmic tremor builds up to a cre-
cendo, often of considerable violence. A
pid movement will arrest the tremor, only
or the cycle to begin again in the new pos-
re. Eventually, these involuntary move-
ents become totally incapacitating.

Abnormalities in the reflexes are rare, and
ralysis and sensory loss do not occur. It
probably on this account that there is often
extreme reluctance on the part of observers unfamiliar with the disease to accept the symptoms as organic. Many patients are regarded as hysterical and may be subjected to the full rigors of modern psychiatric treatment before the diagnosis is established. However, the clinical picture is sufficiently distinctive and, in addition, the majority of patients display the pathognomonic sign of the Kayser-Fleischer ring.[16, 27] This consists of a deposit of golden-brown opalescent pigment, forming a ring about 2 mm. wide just internal to the limbus on the posterior surface of the cornea. It is readily visible to the naked eye, using oblique light, and occurs in no other condition. Pigmentation of the skin is much more rare but was the starting point of the investigation of the pathogenesis of the disease.

The course of the disease varies from a few weeks[26] to 41 years[29] but is usually from 1 to 3 years in the more acute type. Symptoms of hepatic disease may supervene at any stage but are seldom obtrusive. Death occurs from infection, inanition, hepatic coma or from a sudden increase in neurologic signs and coma of unknown cause.

PATHOLOGY

Cirrhosis of the liver is an invariable finding at autopsy, even in cases where in life there was no evidence of hepatic disease. Neither the gross nor the microscopic appearance of the liver presents any distinctive features except possibly for an excess of brown pigment in the hepatic cells. The condition is essentially a multilobular cirrhosis, but the appearance of the liver varies greatly from case to case, according to the duration of the disease and its terminal activity. Accounts of this type of cirrhosis will be found elsewhere in this volume and need not be elaborated here. The spleen is often enlarged and fibrosed.

In chronic cases of the pseudosclerotic type the brain may show little macroscopic change, but in the more acute type very characteristic appearances are found. The most constant finding is symmetrical softening and even cystic cavitation in the putamen of the lenticular nucleus, sometimes extending into neighboring structures. Similar softenings may be found in the caudate nucleus, the thalamus, the cerebral cortex and elsewhere, but these are inconstant and do not occur in the absence of changes in the lenticular nucleus. In more chronic cases softening does not occur, but the lenticular nucleus may appear shrunken and pigmented. It was in this type of case that Hösslin and Alzheimer[25] first described the changes in the neuroglia which were thought to be characteristic of this disease. There is a general increase in astrocytes with a number of abnormal giant forms with pale lobulated nuclei. Other abnormal forms are slightly smaller round or oval cells with vesicular nuclei, and neither type produces fibrils. These glial changes are accompanied by loss of nerve cells which is often extreme in the most affected areas. Later, the Alzheimer glia cells were recognized in the more acute form of the disease.[40] Recently, it has become clear, however, that these cells are not pathognomonic of hepato-lenticular degeneration but are found regularly in patients dying in hepatic coma,[1, 18] although in such patients the changes are le pronounced. The significance of this findi will be discussed in a subsequent sectio The degenerated astrocytes with cytoplasm vacuoles found by Opalsky[34] in hepato-le ticular degeneration have not been report in cases of hepatic coma, but, as far as known at present the microscopic appearan of the brain differs only in degree from th of patients with neurologic complications hepatic cirrhosis.

The Kayser-Fleischer ring consists of layer of pigment in Descemet's membrane the posterior surface of the cornea. Probab insufficient attention has been paid to oth organs, and no characteristic changes ha been described.

PATHOGENESIS

The remarkable and constant associati of cirrhosis of the liver with a familial " generative" disease of the nervous syste naturally aroused great interest as it seem that here, at last, might be found a mo hopeful concept of at least one such disea than premature senescence of neurons. T hope has not been belied, and the gradu unfolding of our as yet imperfect knowled makes a most fascinating study.

Many authorities inclined to the view t the cirrhosis was the primary lesion, and t the cerebral disease was secondary to so toxic effect from the liver. This theory cann be dismissed immediately and has receiv some support from recent interest in the n rologic symptoms sometimes occurring hepatic cirrhosis[1] or after portacaval an tomosis.[38] In addition to the similarity cerebral pathology described in the preced section, there is some clinical similarity, the tremor sometimes seen in these patie bears a strong resemblance to that in more chronic type of hepato-lenticular generation. It is probable that some con sion has arisen in the past and some do has been thrown on the validity of hepa lenticular degeneration as a clinical entit However, patients with a neurologic disor secondary to cirrhosis do not have a corn ring, and the condition is not familial.

hough much remains to be discovered about he relationship between liver and brain, here is a rapidly increasing body of evidence hat a highly specific metabolic disorder underlies both the hepatic and the cerebral esions of Wilson's disease.

The first hint of this disorder was provided n 1913 by Rumpel[36] who, while investigatng the possibility that the pigmentation ometimes seen in this disease might be due o argyria, reported as an incidental finding n accumulation of copper in the liver and he kidney. In the medical jargon of his day e suggested that the disease might be due o "auto-intoxication" with this element. iemerling and Oloff[39] later reported a case n whom, in addition to corneal rings there ere bilateral cataracts of the type produced y copper containing foreign bodies in the ye. Rumpel's observations were repeated,[17, 1, 29] but it was not until 1948 that Cumngs[11] in a controlled study established that here is a considerable excess of copper in he liver and the brain, particularly in the asal ganglia, values in both organs being approximately 10 times higher than normal. ome increase in copper content in the liver ay occur in cirrhosis[11, 13] but not to the egree found in hepato-lenticular degeneraon, and the copper content of the brain in irrhosis is not increased. Recently, the pigent of the corneal ring has also been shown y histochemical means to react strongly for opper.[8]

As will be seen, further evidence of disrdered copper metabolism was soon disovered, but these findings must be viewed gainst our scanty knowledge of the normal, nd it is essential to summarize the relevant acts, many of which were established only n the course of investigating this disease. opper is a "trace element," essential for fe; but only 2 mg. a day is sufficient to aintain a positive balance.[9] The body contains about 150 mg. with a relatively high oncentration in the liver. The plasma coper is approximately 100 μg. per 100 ml. 86-161 μg.) and the greater part is bound n a specific α_2 globulin, ceruloplasmin. This opper will only react with sodium diethyl ithiocarbamate after treatment with acid nd is referred to as the indirectly reacting copper as opposed to the small proportion that reacts directly[19] and which is also bound to protein. A minute fraction exists in a form capable of passing the glomerulus,[15, 33] thus accounting for the traces present in normal urine (usually less than 100 μg. per 24 hours). Ceruloplasmin is an enzyme with an oxidase activity, but its normal substrate and function are unknown.

Following ingestion of radiocopper, absorption curves show a peak at 1 to 2 hours.[15, 32] Newly absorbed copper is attached to the albumin fraction in the plasma but is transferred rapidly to ceruloplasmin.[5, 15] The existence of a mechanism preventing overabsorption on a high dietary intake can be inferred from collected balance data,[9] but nothing is known of factors controlling absorption. Once absorbed, copper is excreted slowly in the bile and also probably through the intestinal wall.[35]

Copper metabolism in Wilson's disease diverges from the normal in many respects. The urinary excretion is increased greatly, and over 1 mg. may be excreted in 24 hours. This was first reported as a chance finding[31] but since then has been confirmed in nearly every case investigated. This increased excretion is highly specific for the disease and, in the absence of proteinuria, has not been reported in any other condition.[13, 33] At the same time the copper content of the feces is much diminished so that, in spite of the loss in the urine, patients with hepato-lenticular degeneration are in strongly positive copper balance while on a normal intake.[52]

Probably of fundamental importance was the discovery of Scheinberg and Gitlin[37] that there is a constant deficiency of ceruloplasmin. Subsequently, this has been confirmed, and it is now known that the plasma copper is characteristically low[4] except in cases where hepatic disease has led to an increase in plasma globulin when high values are sometimes found.[17, 33] As a result, newly absorbed copper remains attached to the albumin fraction and is not transferred to the indirectly reacting fraction.[5, 15] The most important evidence of the significance of these findings in the pathogenesis of the disease is the remarkable effect of treatment with 2,3-dimercaptopropanol (BAL) reported by

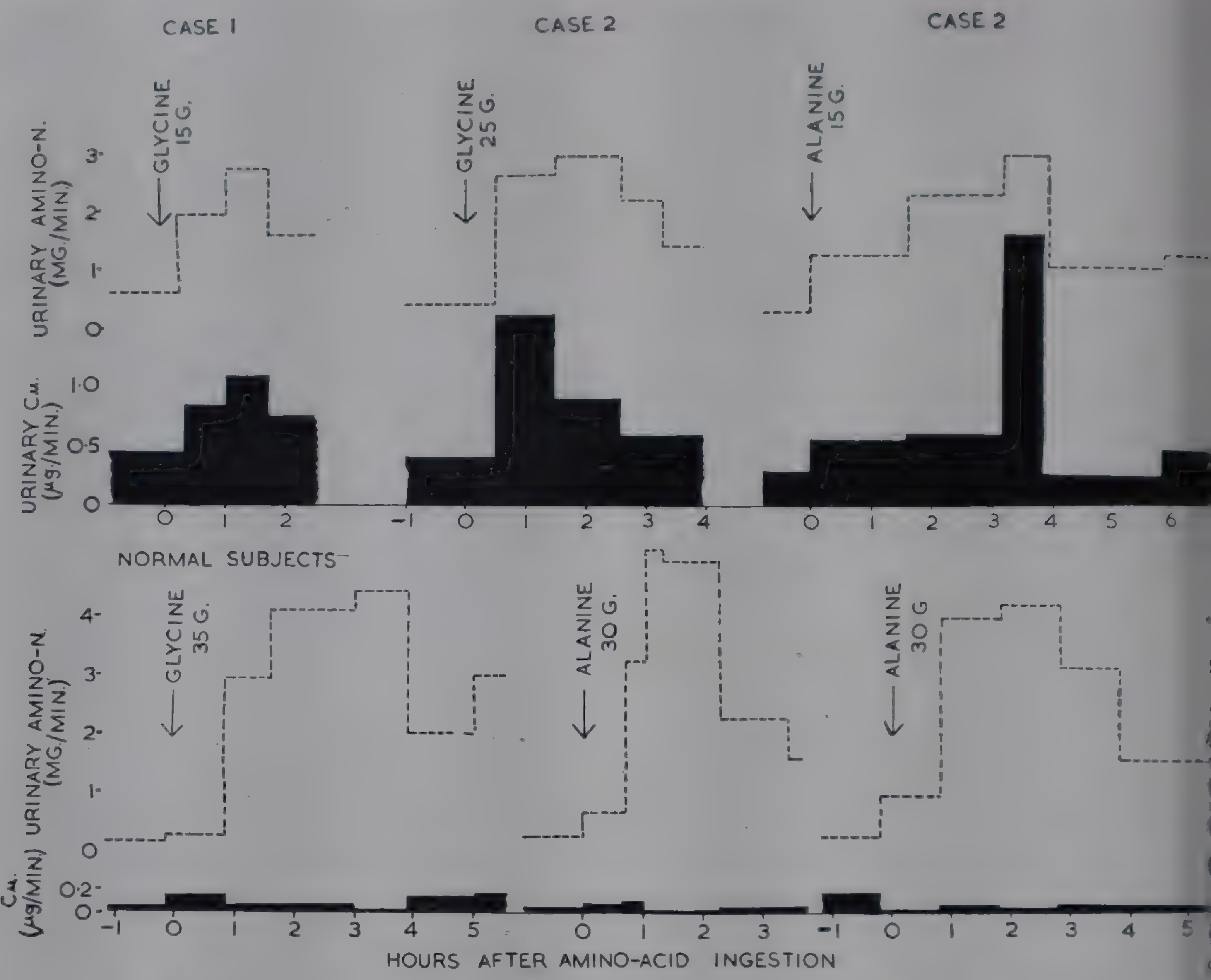

FIG. 147. Effect of ingestion of glycine and alanine on urinary amino-nitrogen (broken line) and on urinary copper (black rectangles). Cases of hepato-lenticular degeneration above; 3 normal subjects below. (Matthews, W. B., Milne, M. D., and Bell, M.: Quart. J. Med. **21**:425)

Cumings[12] and Denny-Brown and Porter.[14] A further considerable increase in urinary copper was followed by slow but unmistakable and sometimes astonishing clinical improvement.

However, in 1948 a second, apparently unrelated metabolic abnormality had been discovered by Uzman and Denny-Brown[44] who reported the presence of amino-aciduria which is now known to be present in nearly every case. It has been found also in younger siblings of known cases but so far only in one family.[24] The amino-aciduria is not secondary to elevation of the plasma levels due to liver disease as was suspected at first, as total plasma levels are normal, and individual acids are present in normal concentration.[41] It has been shown by artificially raising the plasma levels of amino-acids that the rate of urinary excretion is much greater than in normal subjects at similar plasma levels,[16] and therefore the amino-aciduria is renal origin, due to a tubular reabsorption defe A similar defect is sometimes present glucose, leading to renal glycosuria.[10] T amino-aciduria involves most of the ac normally excreted but to differing degre the increase in threonine and cystine be proportionately the highest, while prol and citrulline, not normally excreted, may present in considerable quantities.[41] Amo those investigated, the excretion of meth nine is probably normal.[33, 41] More recen Uzman and Hood[45] have discovered the pr ence in the urine of specific oligopepti with terminal dicarboxylic acid residues.

The possible interconnection of the c order of copper metabolism and the amin aciduria was investigated by Matthews, Mi and Bell,[33] who found that increasing mino-aciduria by means of large oral doses f glycine or alanine produced a prompt inrease in urinary copper (Fig. 147). There vas, in fact, a fairly close correlation between he power of the urine to bind copper, due nainly to amino-acids, and the amount of opper actually present. Bearn and Kunkel[6] ave shown that copper excretion rises with ncreased dietary protein and bears little reation to the intake of copper. Cortisone, vhich increases the amino-aciduria, also proluced a parallel rise in copper excretion. It vas suggested that the copper might be exreted as chelation complexes with the aminocids and that a tubular reabsorption defect night exist for such complexes.[38] Uzman[43] has been able to show that this is not so and that most of the copper in the urine is combined with the peptides he had discovered previously. He suggested that these copper-peptide complexes competed for reabsorption in the renal tubule with amino-acids, so that artificially increasing the concentration of the latter would interfere with reabsorption of the copper complexes.

Knowledge has accumulated very rapidly in the last few years, and it is not surprising that there is no generally accepted theory of the pathogenesis of the disease. Basically, there are two schools of thought. According to one theory the fundamental defect is a congenital failure to synthesize ceruloplas-

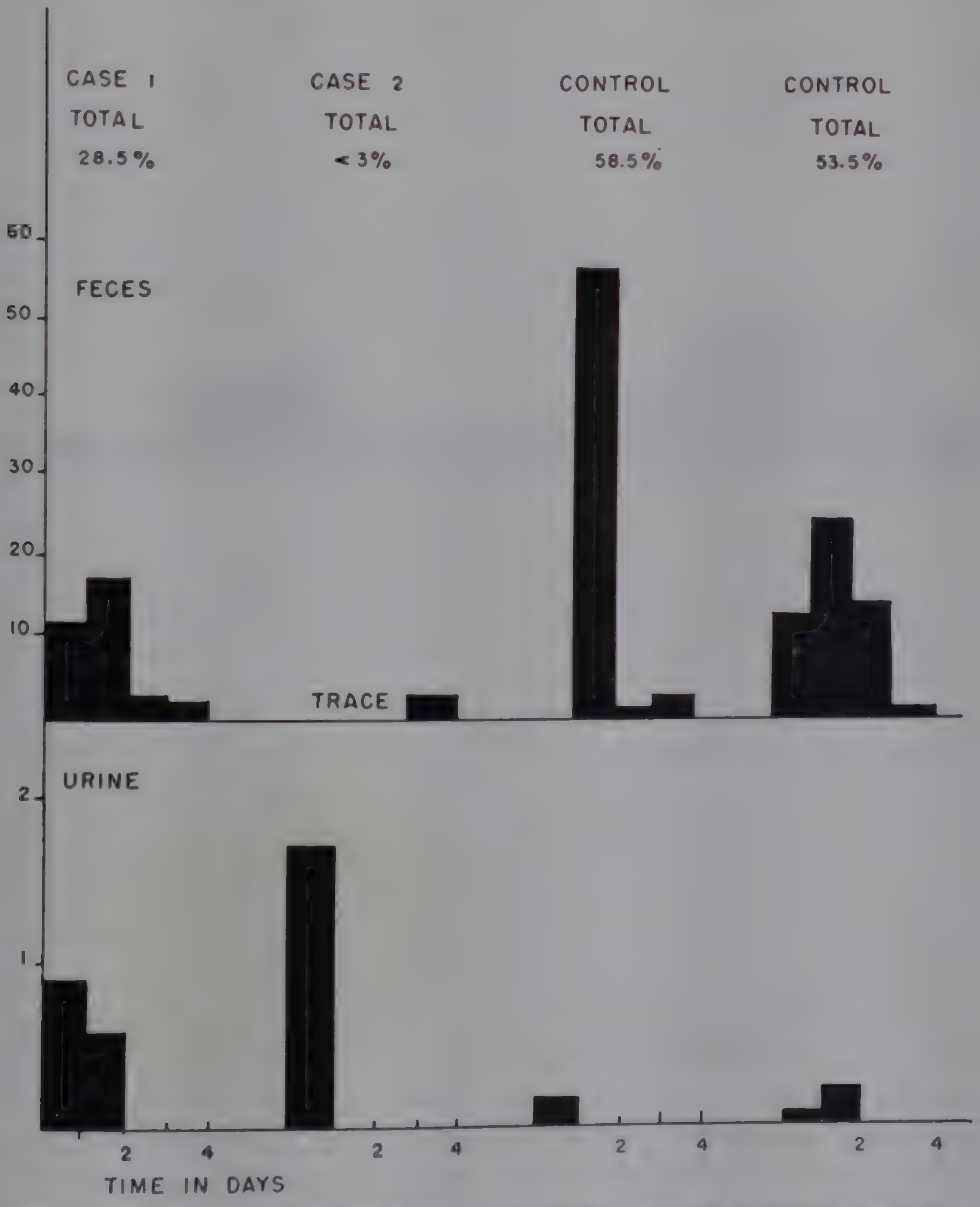

FIG. 148. Recovery in the urine and the feces of a single oral dose of 4.95 mg. of copper labeled with Cu^{64} in hepato-lenticular degeneration and in normal subjects. (Matthews, W. B.: J. Neurol., Neurosurg. & Psychiat. 17:242)

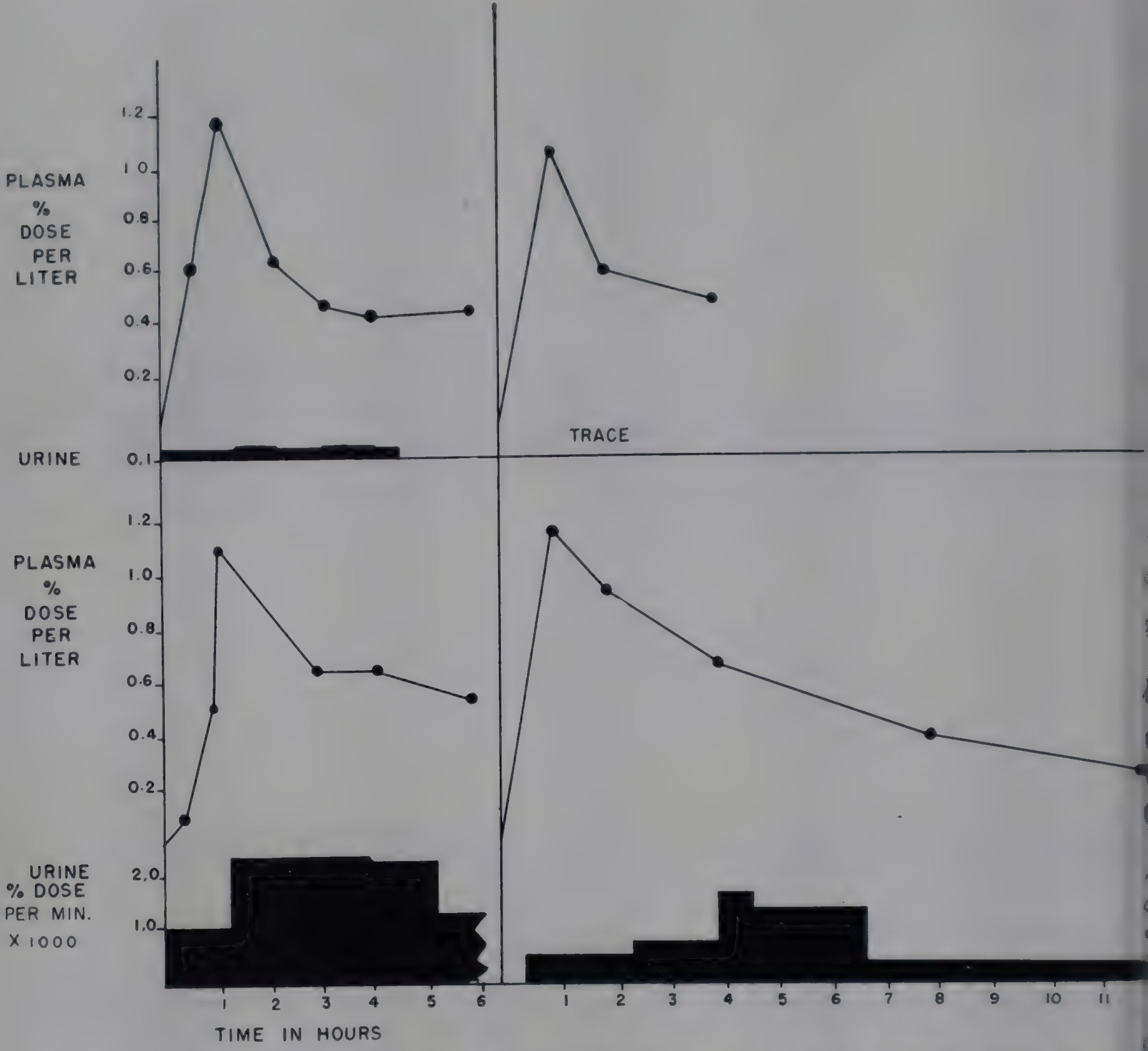

FIG. 149. Plasma and urine levels following ingestion of 1.2 mg. of copper labeled with Cu^{64}. Two cases of hepato-lenticular degeneration below; two controls above. (Matthews, W. B.: J. Neurol., Neurosurg. & Psychiat. 17:242)

min, leading in some way to lifelong overabsorption of copper. The hepatic and the cerebral lesions and the amino-aciduria and the abnormal peptides are all the result of copper poisoning, and the increased urinary copper is due to a unique combination of excess tissue copper and a renal failure to reabsorb copper-peptide complexes.[4, 14, 33] Objections to this attractive theory may be the result of incomplete knowledge but are important, as neither the congenital nature of the ceruloplasmin deficiency[22] nor the overabsorption of copper have been proved. Matthews[32] investigated the fate of single oral doses of radiocopper and found evidence suggestive of overabsorption (Fig. 148), b
results were not conclusive in a small ser
of patients. Absorption curves in the plas
were almost identical in the patients and
the controls (Fig. 149).

An alternative theory advanced
Uzman[43] is that of a congenital defect
proteolytic enzymes leading to the presen
in the tissues of specific peptides with
strong affinity for copper and therefore
secondary accumulation of this element. T
specific peptides have been found in the uri
of younger asymptomatic sibs of kno
cases[45] in the absence of increased cop
excretion, but the nature of the plasma c

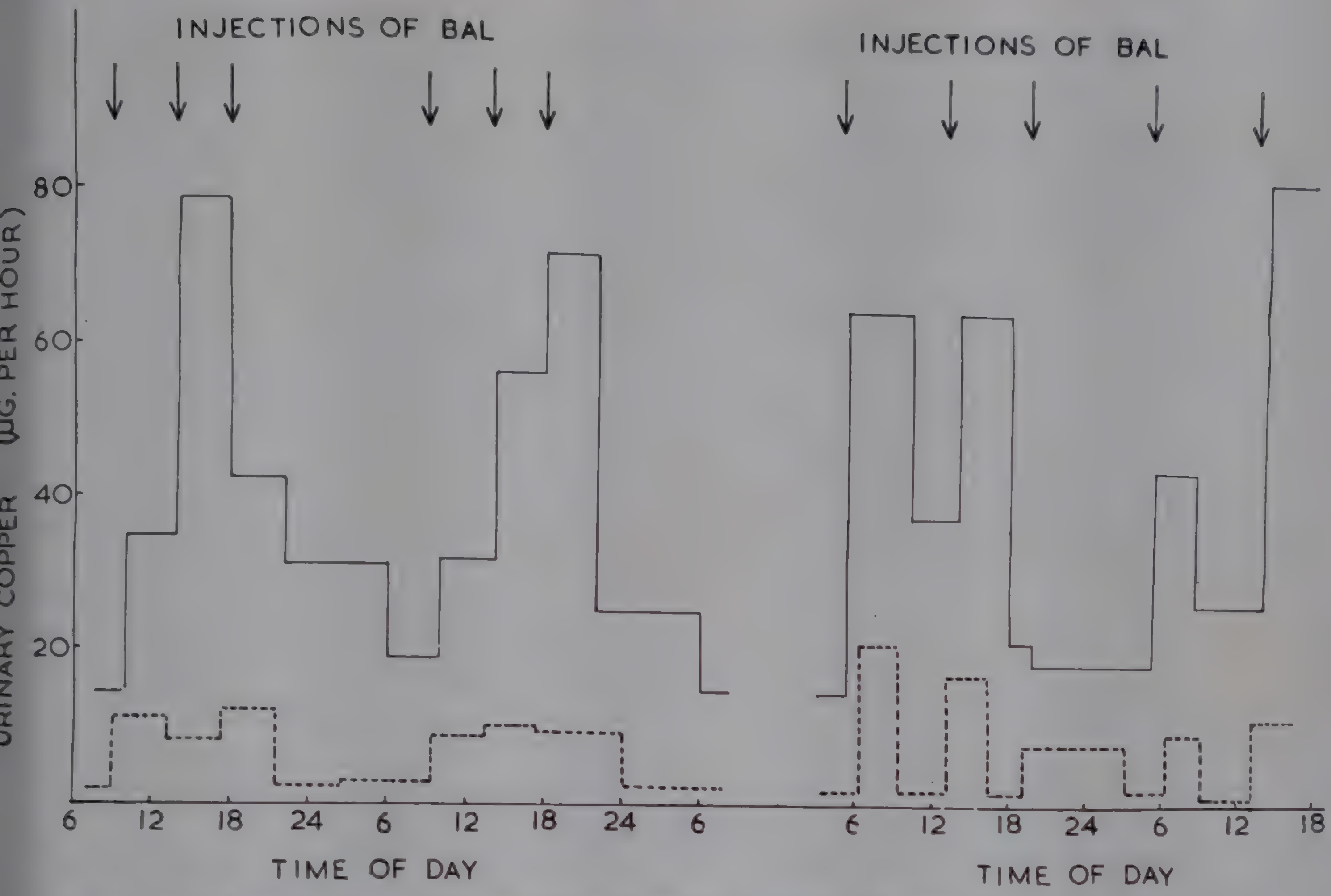

FIG. 150. Urinary excretion of copper after injections of BAL in a case of hepato-lenticular degeneration (continuous lines) and in two normal subjects (broken lines). (Matthews, W. B., Milne, M. D., and Bell, M.: Quart. J. Med. 21:425)

er was not investigated in these patients, nd the congenital nature of the abnormality as not been demonstrated. Again, many ital facts are unknown, in particular the orm in which the excess copper is present n the tissues. Much of it does not seem to e bound very firmly as it can be extracted eadily by means of BAL (Fig. 150). There no evidence that copper is removed from ne plasma by the tissues unduly rapidly, and ne problem of retention of copper and diinished intestinal excretion as opposed to verabsorption as a cause of the positive balnce remains to be settled. The copper content of the bile is known to be normal, at ast in single specimens,[14] but the intestinal xcretion of injected radiocopper has been ported to be less than normal.[5]

It is unlikely that any hypothesis now adanced will remain long unchallenged, but e evidence that the fate of newly absorbed opper is abnormal in hepato-lenticular deeneration[5, 15] is in favor of a primary disorder of copper metabolism. Similarly, there is no doubt that the symptoms of the disease are to some extent reversible by the removal of copper. It is possible that the presence of abnormal copper-binding peptides is the result of a failure to synthesize the normal copper-binding protein. Newly absorbed copper cannot be transferred to ceruloplasmin and is bound in other ways, either in the tissues or in the plasma, leading to accumulation in the former and to an increase in the filtrable fraction in the latter and increased urinary excretion (Fig. 149). The hepatic and cerebral lesions are then the direct result of copper poisoning and the amino-aciduria, either the result of competition for reabsorption with the peptides or a toxic effect of copper on the renal tubules as in lead poisoning.[50] The views of Mallory on the pathogenesis of cirrhosis will be recalled.[30] The basal ganglia are peculiarly liable to accumulate such substances as calcium and iron and also are unduly susceptible to the toxic action of mercury and manganese. It seems likely that copper is treated similarly, and that any general excess will lead to a disproportionate local accumulation in the basal ganglia. Copper is a potent enzyme poison, but the only hint as to its possible mode of action in hepatolenticular degeneration comes from the report of a very advanced case in whom there was a defect of oxygen uptake by the tissues of such degree that venous blood appeared bright red.[51] A similar disturbance maximal in or localized to the basal ganglia in less advanced cases might produce the characteristic lesions of the disease. Indeed, the "autointoxication" of Rumpel[36] may be not far from the truth.

TREATMENT

A high-protein diet appears to be of some value if hepatic disease is clinically obvious but has no effect on the course of the nervous symptoms, although such a diet has been shown to increase copper excretion.[6] Choline and methionine supplements are also valueless.[23, 33] Cumings[12] and Denny-Brown and Porter[14] introduced the treatment of Wilson's disease with BAL. In Cuming's cases, although a great increase of copper excretion was produced, clinical benefit was doubtful, but Denny-Brown and Porter reported remarkable improvement. They eventually found that from 1.25 to 2.5 mg. of BAL per kg. body weight twice a day for 10 days was the most satisfactory dosage, the course being repeated at intervals of 1 month and then 2 months. Such a course may be given without toxic effects, and approximately 12 mg. of copper above the resting level may be excreted over a 10-day period. Copper balance, previously strongly positive, becomes negative during treatment, but the excess of excretion over absorption may not be very great.[52] The biochemical response lessens in succeeding courses but remains obvious. Copper appears to be much more readily mobilizable with BAL than in normal subjects (Fig. 150), and the lessening response presumably is due to depletion of this more loosely bound fraction.

It is not to be expected that patients of the more acute type of the disease with seve destructive lesions in the brain will show a response to treatment, and they do not c so. In the more chronic type of case real remarkable improvement may occur, inc pacitating tremor being reduced to a lev compatible with normal life.[7] This improv ment is not immediately apparent but ma begin only after several courses have bee given without obvious benefit. No toxic e fects of BAL on the liver have been report in these cases and, in view of the hopele prognosis without treatment, overt hepat disease is not a contraindication. Liver-fun tion tests do not usually improve, but o case is reported with hepatic symptoms or in whom nearly all evidence of disease d appeared under treatment.[46] An interesti indication of the depletion of copper in t body is fading of the corneal ring,[14] but th has not been evident in personally observ cases.

Treatment with BAL, although a mo notable advance, cannot be regarded as unsurpassable ideal. The injections can painful and usually involve admission to ho pital, and treatment presumably must be li long. Large oral doses of glycine, while p ducing an increase in copper excretion, not influence the symptoms over a period several months. Future advances may lie the development of a combined attack signed to prevent the absorption of cop and to remove copper from the body. T chelating agent "Versene" (calcium disodi salt of ethylenediaminetetra-acetic ac greatly increases copper excretion when giv intravenously but unfortunately is ineff tive by mouth.[6] It is also possible to establ a negative copper balance by means of ion exchange resin which hinders the abso tion of copper.[52] The prophylactic treatm of younger sibs of known cases who show characteristic biochemical abnormalities not yet been explored. Diagnosis at the st of the "biochemical lesion" and before irr arable damage has occurred is the first sential for successful treatment. Only increased awareness of the existence of remarkable disease and by recognition unfamiliar symptoms may yet be organic this be achieved.

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hapter 19

THE LIVER IN CIRCULATORY FAILURE

Sheila Sherlock, M.D.

The hepatic veins enter the inferior vena va very close to its entrance into the right ricle, and a rise in pressure in the right ricle is transmitted readily to the hepatic ins. Liver cells are particularly vulnerable oxygen deprivation; therefore, diminished patic oxygen supply consequent upon a iling heart or lowered blood pressure is flected in impaired function of liver cells. epatic dysfunction is to be expected in both ripheral circulatory failure with a lowered ood pressure and in right-sided congestive art failure, with a rise in right auricular essure or lowered cardiac output.

HEPATIC CHANGES IN ACUTE HEART FAILURE AND SHOCK

Hepatic changes occur in shock states of most any cause and are particularly comon with myocardial infarction,[12] with acute art failure of all types and in many other nditions, including crushing and severe uma, burns, hemorrhage, sepsis, pulmory embolism, peritonitis and blackwater ver.[8, 14, 55]

Pathologic Changes

Pathologic changes follow the same patn, whatever the cause of the shock.

Macroscopically the liver appears to be rmal.

Histologic features are:

1. Congestion of the central hepatic vein th local hemorrhage from it (Fig. 151).
2. Focal necrosis of liver cells which is ually centrilobular but occasionally may pear to be mid-zonal, perhaps due to the ction being cut in a plane that missed the jacent central vein.
3. The necrotizing liver cells take eosin ins in contrast with the basophilia of normal liver cells. The cytoplasm may show hydropic change, reminiscent of that observed in carbon tetrachloride poisoning, but fatty change is not seen.
4. Nuclear changes in the necrotic zone are prominent, with pyknosis and disintegration and fading of the nuclei (Fig. 152).
5. There may be polymorphonuclear infiltration around the focal necrosis.
6. The essential reticulin structure of the liver is preserved within the necrotic zone.[12]

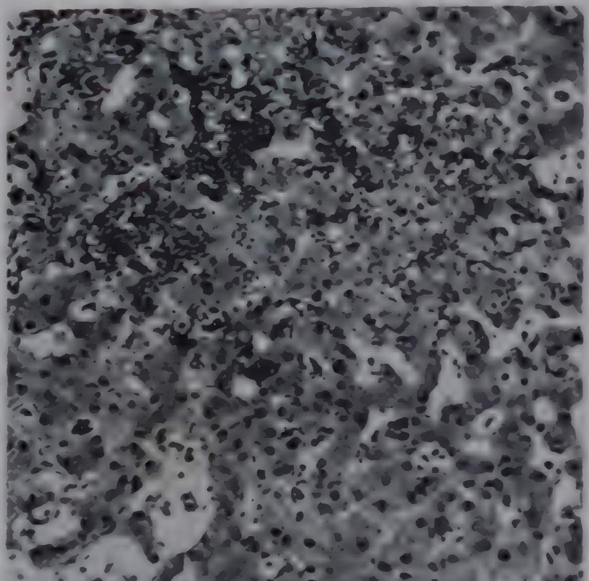


Fig. 151. Ischemic heart failure. Serum bilirubin 2.1 mg./100 ml. Liver cells have disappeared from the center of the lobule and are replaced by frank hemorrhage (H.E. × 120). (Sherlock, S.: Brit. Heart J. 13:273)

7. With recovery from the shock, particularly in traumatic cases, mitoses may be prominent in the hepatic cell nuclei.[8] This may represent part of the reparative process.

8. Sometimes, and for no obvious reason, the left lobe of the liver may suffer more than the right. This is similar to that seen in acute viral hepatitis where the left lobe also may be more necrotic than the right.[30]

TOXIC AND CONGESTIVE CENTRAL HEPATIC NECROSIS

Wallach and Popper[55] analyzed the clinical and the gross anatomic findings in 100 patients in whom autopsy revealed central hepatic necrosis (not including primary hepatic disease). Two main groups could be recognized, depending on whether or not congestive heart failure was present. Histologic changes in the heart failure or "congestive" cases included large central veins with wide branches piercing through the walls of the larger vessels, marked disappearance and atrophy of the liver cells, but no fragments nor remnants of cells and, usually, dilatation of sinusoids. The "toxic" cases were distinguished by fragmentation of the nucleus, exudative cells encircling the affected cells, and, despite occasionally wide sinusoids, small central veins with narrow pierci branches and dissociation of liver cell cor These differences might be related to t increased venous pressure in the congesti cases and the presence of a circulating i jurious substance in the toxic instances.

PATHOGENESIS OF HEPATIC CHANGES

The extent of the changes can be relat to the duration of the shock state; if it exi longer than 24 hours, hepatic necrosis is most constant; if less than 10 hours, it unusual.

The fall in systemic blood pressure is t most important factor in causation. With t fall in blood pressure there is a fall in t blood flow through the portal vein on whi the liver mainly depends for its oxygen su ply. In addition, the dropping blood pressu proportionately lowers the oxygen content the portal venous blood.[32] Therefore, the h patic cells are more dependent for oxyg on the hepatic arterial blood flow. Howev this is reduced also as a result of vasoc striction consequent on the fall in syster blood pressure. Therefore, the hepatic ce are anoxic, and the cells at the center of lobules, which receive blood at a lower o gen tension than at the periphery[1] and

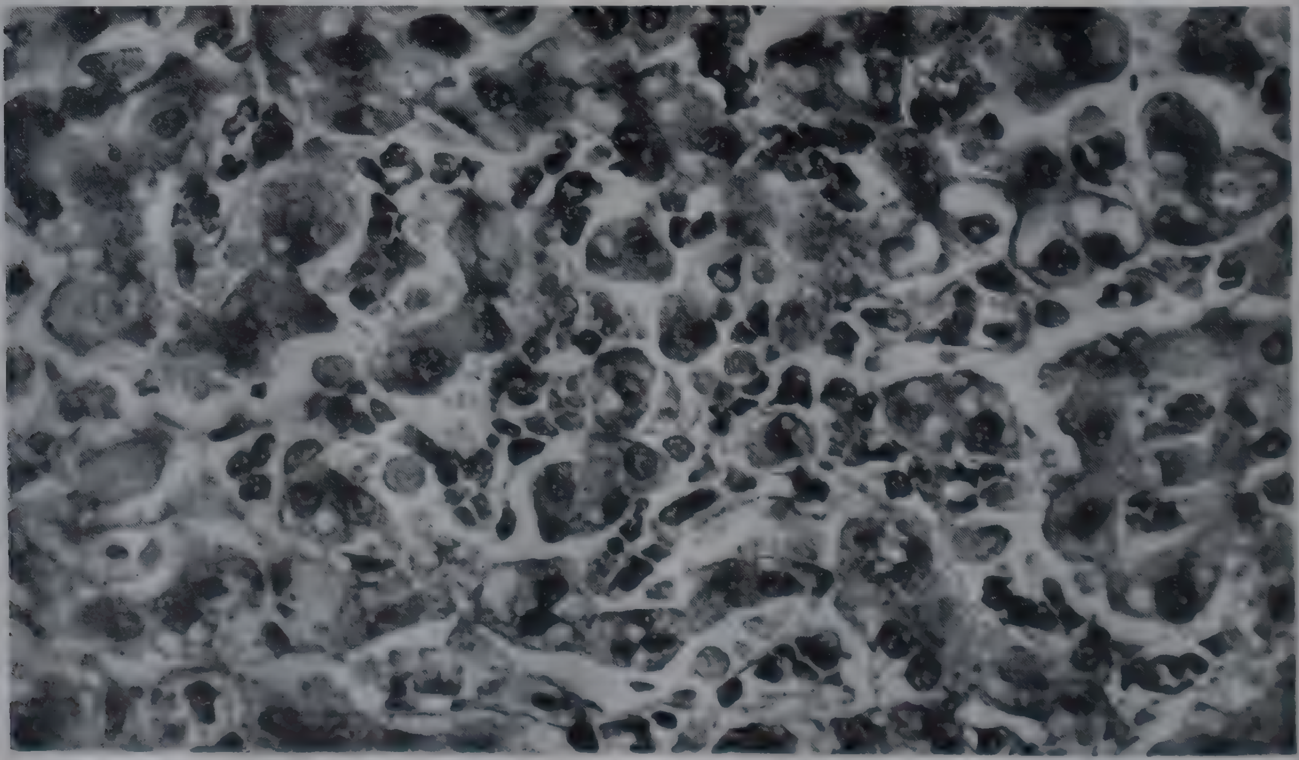


FIG. 152. Crushing injury. Shrinkage of liver cells with nonfatty vacuoles appearing in cytoplasm and nonfatty globules lying free between cells and sinusoids (H.E. × 430). (Bywaters, E. G. L.: Clin. Sc. 6:19)

nore susceptible to a fall in the oxygen suply to the liver, become necrotic.

In the dog the outflow of blood from the iver is controlled by a sluice mechanism ocated near the caval orifices of the main epatic vein.[2] Contraction of muscles in the valls of hepatic veins in this area causes iminution of outflow of blood from the liver, vhich swells. Active constriction of hepatic enous radicles in man has been postulated o that the intralobular blood flow is imeded. This is put forward as a significant actor in the pathogenesis of the centrilobular esions occurring in anaphylactic shock, in lackwater fever (malignant malaria) and n congestive heart failure.[35, 36] However, this nechanism never has been demonstrated in nan and seems to be unlikely, for in man he hepatic veins have little plain muscle in heir walls.[41]

He Liver and the Metabolic Changes Occurring in Peripheral Circulatory Failure

Results have been based largely on obervations of experimental animals, and it as been shown clearly that the liver in shock unctions abnormally.

1. It is unable to store glycogen normally nd to convert lactate and pyruvate to glycoen.[19]
2. The oxygen consumption of liver slices rom shocked animals is diminished.[45]
3. There is a failure to deaminate aminocids with a rise in the blood amino-acid itrogen content.[57]
4. In experimental shock two vasotropic rinciples, one renal (VEM), the other of epatic (VDM) origin, may participate.[52] 'EM is a renal vaso-exciter substance which eads to development of hyperreactivity in eripheral small vessels with the enhancenent of constrictor activity. Thus it is comensatory in nature and assists in the mainenance of an adequate circulation in the face f a reduced blood volume. However, if the asoconstriction is sufficiently profound and rolonged, VEM disappears from the blood tream and is superseded by the appearance f the hepatic vasodepressor material VDM) which exhibits an opposite decomensatory type of behavior. It has been postulated that the initial vasoconstriction of shock may be mediated by VEM and the terminal, irreversible vasodilatation, by VDM.

There are a few observations along similar lines in shock in man. Davidson and his coworkers[13] noticed a rise in the level of the blood lactic acid and alpha-amino nitrogen in medical shock, and some of their patients also showed mild icterus and an increase in the prothrombin time. All these suggested hepatic involvement. Bywaters[8] also observed jaundice in some of the severely traumatized patients whom he studied.

EXPERIMENTAL CHRONIC HEPATIC VENOUS CONGESTION

In the experimental animal, individual ligation of all the hepatic veins is impossible, and the usual method is to constrict the inferior vena cava by a cellophane band placed above the entry of the hepatic veins, thus obstructing the venous return from the liver.

Structural Changes

Structural changes in the liver[6, 7, 24, 53, 58] are essentially similar to those seen in congestive heart failure. The whole liver swells, and the hepatic veins dilate with congestion of the sinusoids. Centrilobular hemorrhage and necrosis of liver cells follows, and the extent is proportional to the amount of hepatic venous obstruction. Connective tissue proliferates round the central vein, giving a picture analogous to cardiac cirrhosis. The liver cells adjoining the portal tracts are well preserved, and the tracts themselves show little change. In acute hepatic venous occlusion the lymphatics are greatly dilated but this later subsides.

Functional Changes

Functional changes in the liver include the accumulation of ascites. It has been suggested that this ascites forms by outpouring of hepatic lymph into the peritoneum. Increased liver lymph flow is the first sign of venous congestion of the liver,[7] and in the dog occlusion of the hepatic venous return results in a 10- to 20-fold increase of liver lymph flow having a high protein content.[54] The hepatic sinusoids are related intimately to the hepatic lymphatics, and the increase in sinusoidal pressure may be related to the overproduction of lymph. Although there is an undoubted increase in hepatic lymph flow, there are no obvious anatomic connections between the liver lymphatics and the peritoneal cavity, and the formation of ascitic fluid from hepatic lymph never has been proved conclusively.

Hepatic venous congestion in the dog results in sodium retention in the ascitic fluid.[47] Two explanations have been offered. The low tissue pressure in the peritoneal cavity may trap sodium and chloride; alternatively, the retention may be a renal compensatory mechanism to offset the loss of body fluids, plasma proteins and electrolytes into the peritoneal cavity. It has even been postulated that the sodium retention of congestive heart failure may be related in part to the hepatic venous congestion occurring in that condition.

Liver-Function Tests

Liver-function tests show little significan
hepatic cellular damage. The plasma non
protein nitrogen, glucose or prothrombin tim
show little change; although the serum pro
tein concentration may fall, this may b
related to loss of protein into the ascite
rather than hepatic cellular dysfunction. I
seems unlikely that the disturbed hepati
function tests in congestive heart failure ar
due to hepatic venous congestion alon
Some other factor must be playing a par
and this may well be the concomitant anoxi
of the liver cells.[24]

THE LIVER IN CONGESTIVE (RIGHT-SIDED) HEART FAILURE

Pathologic Changes

Postmortem hepatic autolysis is partic
larly rapid in the patient dying in heart fai
ure.[42, 50] In the agonal period and in the 1
hours after death, the liver cells disappe

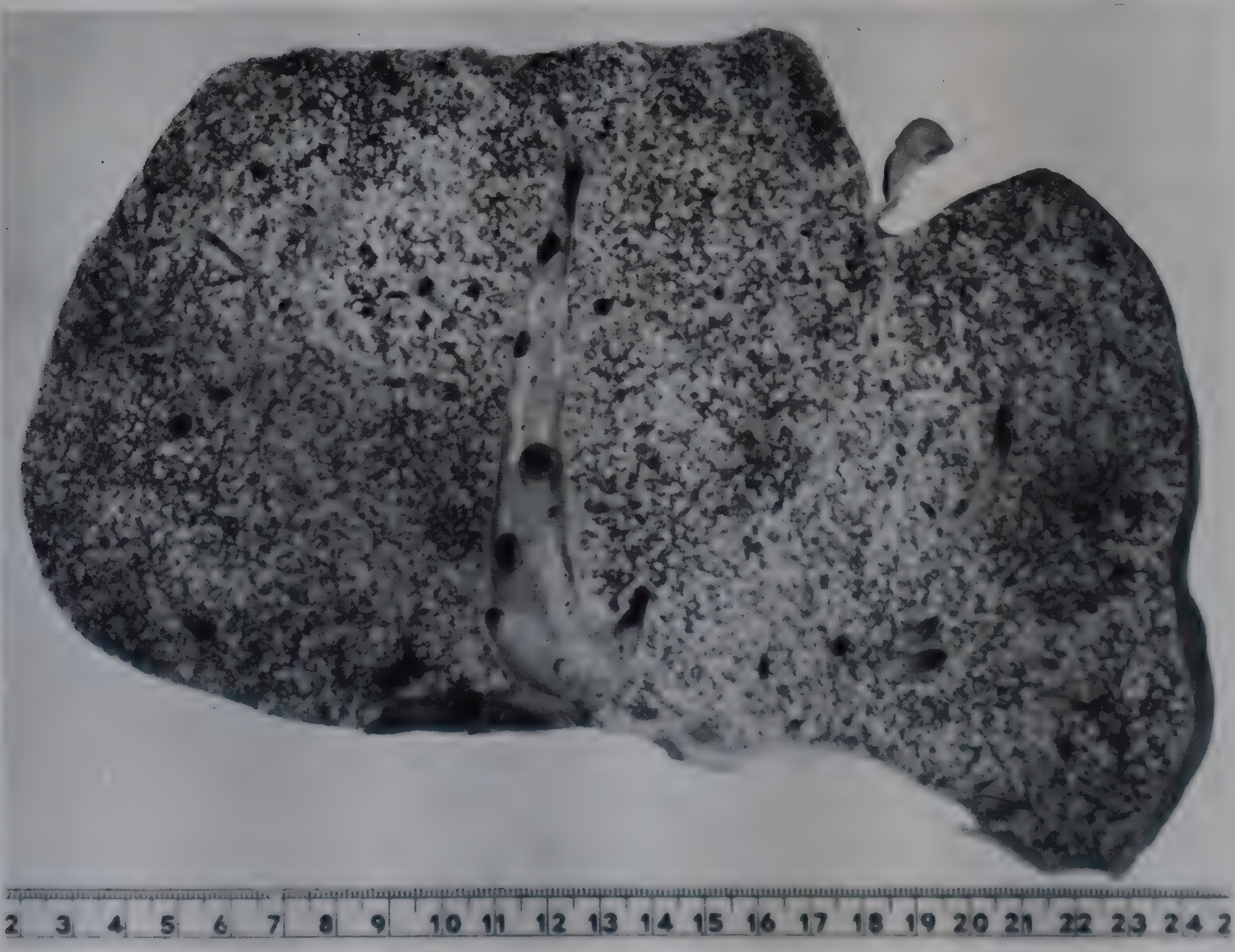


Fig. 153. Cut surface of liver from patient dying with congestive heart failure. Note dilated hepatic veins. Light areas corresponding to peripheral fatty zones alternate with dark areas corresponding to central zonal congestion and hemorrhage.

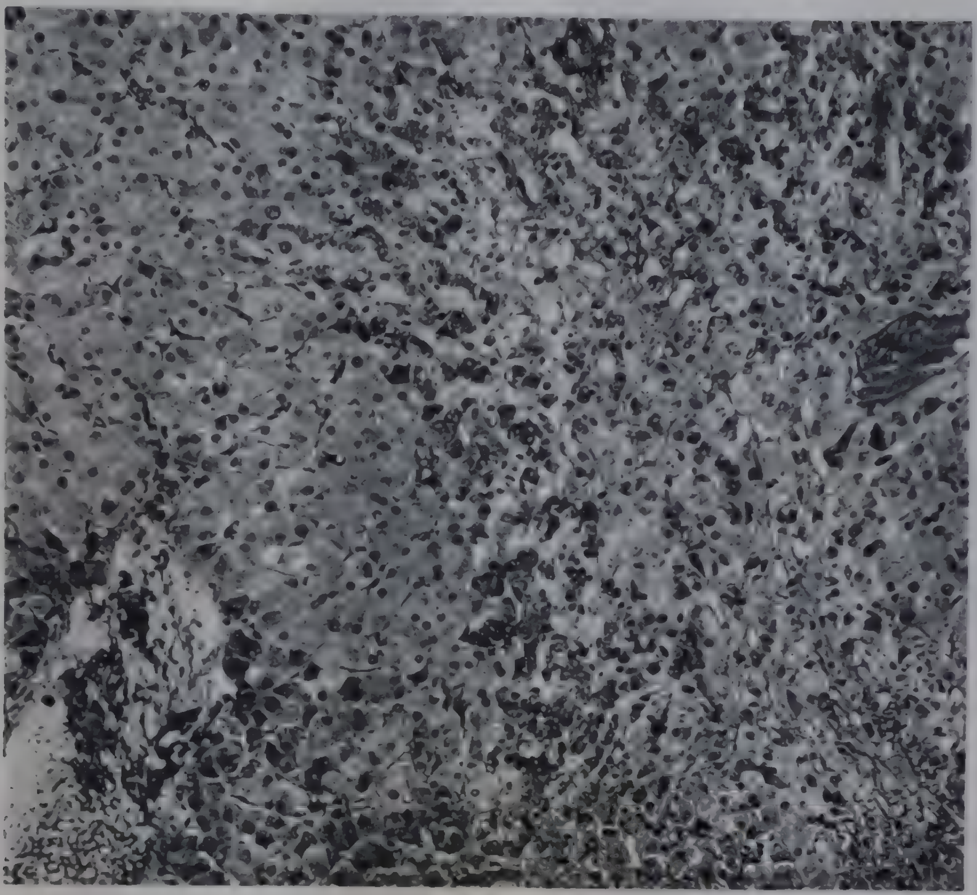


Fig. 154. Cor pulmonale. Serum bilirubin 3.4 mg./100 nl. Gross centrilobular congestion and liver cell necrosis. Pigment increase is seen n the degenerating liver cells. Liver cells at the periphery of the lobule are relatively normal. (H.E. × 120). Sherlock, S.: The liver in ieart failure, Brit. Heart J. 13:273)

nd shrink, and the remaining cells become lissociated from each other. Glycogen is lost rom the liver cells, the parasinusoidal spaces re opened up, and the liver cell columns are hrunken. The sinusoids contain less blood han in life. The appearance of fat in the iver cells in heart failure is also a postmortem phenomenon. Autopsy material is herefore unreliable for the assessment of the ffects of cardiac failure on the liver in life. Accurate histologic data can be obtained only y aspiration liver biopsy. Hemorrhage might e anticipated from the puncture of "congested" liver of heart failure, but 41 biopsies performed in one series and 30 n another were uncomplicated and well olerated.[50, 56]

Macroscopic Changes

At autopsy the liver usually is enlarged, ut liver weights are variable and bear no elation to the clinical assessment of hepatic ize. This may be due to drainage of blood, ostmortem, from an overdistended liver into ther organs. The liver is purplish in color, ith rounded edges. If there is gross fibrosis nd a cardiac cirrhosis, the liver may be small ut it is never so irregular and never has the ame degree of nodular regeneration of liver ells as is seen in a classical Laennec's irrhosis.

The cut surface (Fig. 153) shows prominence of the hepatic veins which may be thickened in a chronic case. The organ drips blood. If a cardiac cirrhosis is present, the liver cuts with the toughness associated with excessive fibrous tissue. The lobules are prominent, with yellow and red areas alternating; the red represents the hemorrhagic centers of the lobules, and the yellow the fatty periphery. This appearance has been likened to a nutmeg.[25] In a long-standing case of heart failure, the red and yellow areas may coalesce, giving the cut surface the appearance of a fern leaf.

Histologic Changes

The general anatomy of the lobule is usually intact, the portal tracts bearing their normal relationship to the central hepatic vein. Sometimes the lobular pattern is reversed, the portal tract apparently lying centrally with a ring of surrounding fibrous tissue passing from central vein to central vein. This is characteristic of cardiac cirrhosis (Fig. 156).

The central vein always is dilated, and the sinusoids entering it are engorged for a variable distance toward the periphery of the lobule (Fig. 154). In severe cases there is frank hemorrhage from the sinusoids with focal necrosis of the liver cells. This may be

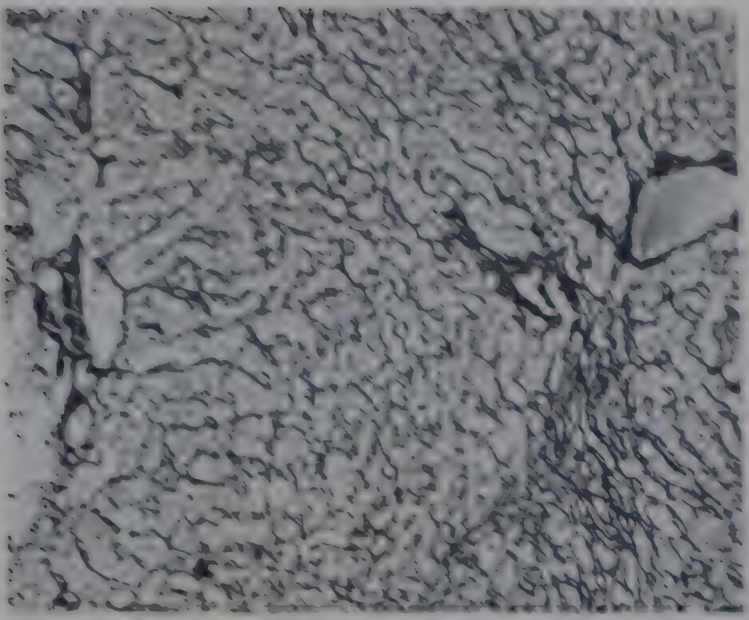


FIG. 155. Same section as in Figure 154. Reticulin stains show condensation at the lobular center (H.E. × 120). (Sherlock, S.: The liver in heart failure, Brit. Heart J. 13:273)

attributed to the lowered blood pressure and shock state. The liver cells columns are usually atrophic, particularly toward the centers of the lobule, and appear to be attenuated. The liver cells show a variety of degenerative changes in the central area. The cytoplasm is shrunken with excessive granularity, and the nuclei show fragmentation and pyknosis, diminishing in intensity as the portal zones are reached. Apart from cardiac cirrhosis the portal tracts are usually normal. Each portal tract is surrounded by relatively normal cells to a depth that varies inversely with the extent of the centrilobular necrosis.

Diffuse loss of glycogen is noted only agonally. Surviving cells usually contain their normal complement of glycogen, and this is true not only of the relatively normal portal zones but also of the surviving liver cells lying amid debris at the center of the lobule. Biopsy sections show significant fatty change in only about one third of sections and then only a few scattered globules, usually at the periphery of the lobule. This absence of fat in material obtained in life contrasts with the usual postmortem picture described in textbooks of pathology.

The liver cells at the center of a lobule contain increased amounts of a brown pigment. In many instances the central degenerating cells are packed with pigment
ules, and as the cell disintegrates compl
the pigment lies free at the center of
lobule amid cellular debris. This brown
ment does not give the Prussian blue rea
to iron, neither does it give reactions
hemofuscin. Sudan 3 stains the granu
rich brown, both in frozen sections and i
form of fixed sections. This suggests tha
pigment is a lipochrome. The pigment
stains green with methylene blue, w
suggests a relationship to bile pigment.

Methylene blue stains sometimes sho
excess of bile pigment in the minute
channels (bile thrombi), especially in
periportal zone. These are usually cons
ous in the deeply jaundiced patients.

COURSE OF CENTRILOBULAR HEPAT CELL NECROSIS

If the heart condition does not respo
therapy, the necrosis spreads towar
periphery of the hepatic lobule. If the ca
failure responds to treatment, the centri
lar necrosis may heal, and even if ther
definite cardiac cirrhosis, hepatic fur
may be adequate.

FIBROUS TISSUE CHANGES AND CARDIAC CIRRHOSIS

In the mildest cases the reticulin p
of the liver is normal. The occasional as
tion of much liver damage with an
reticulin framework in the lobule usu
seen in acute heart failure of short dur
The next stage is centrilobular reticulin
densation. Hepatic cells have been lost
the centers of the lobule, and this h
sulted in collapse of the reticulin stron
very common finding in heart failure.

Then follows centrilobular reticulin
liferation. Not only are the reticulin
more closely packed together but also
is actual production of new reticulin
center of the lobule. This is seen as
yellow fibers in the silver-impregnate
tions (Fig. 155). A centrilobular incre
collagen is found also. The central vein
fibrous thickening of its wall, and i
proliferations with loose connective
fibers may be seen[10] (phlebosclerosis
connective tissue extends outward for

stance but does not reach the periph- the lobule.

he heart failure continues or relapses, nnective tissue from one hepatic vein the connective tissue from the central of adjoining lobules. The portal areas ne surrounded by a ring of fibrous passing from central vein to central This gives the appearance of reversed tion. This lesion is a frank cardiac sis (Fig. 156). The portal tracts may n unaffected, but in longstanding cases they are involved also. The bile ducts erate, fibroblasts are seen, and some- there is also a little round-celled pro- ion. When there are changes in both l areas and portal tracts a complex d" picture results (Fig. 157). This may ficult to distinguish from the usual type of portal cirrhosis. However, careful study usually demonstrates that the maximal fibrosis is centrilobular. In some instances, nodular regeneration of liver cells may be seen, but this is never as conspicuous as that of ordinary Laennec's or portal cirrhosis.

Course of Fibrous Tissue Changes

If the heart failure continues, the fibrosis progresses so that terminally a "mixed" picture of central cardiac and portal cirrhosis is seen. However, if the failure responds to therapy not only does the centrilobular necrosis heal but the cirrhosis regresses, the fibrous tissue bands becoming narrower and acellular. This type of (latent) cardiac cirrhosis may cause no functional hepatic disturbance. If heart failure again supervenes the acute changes again appear.

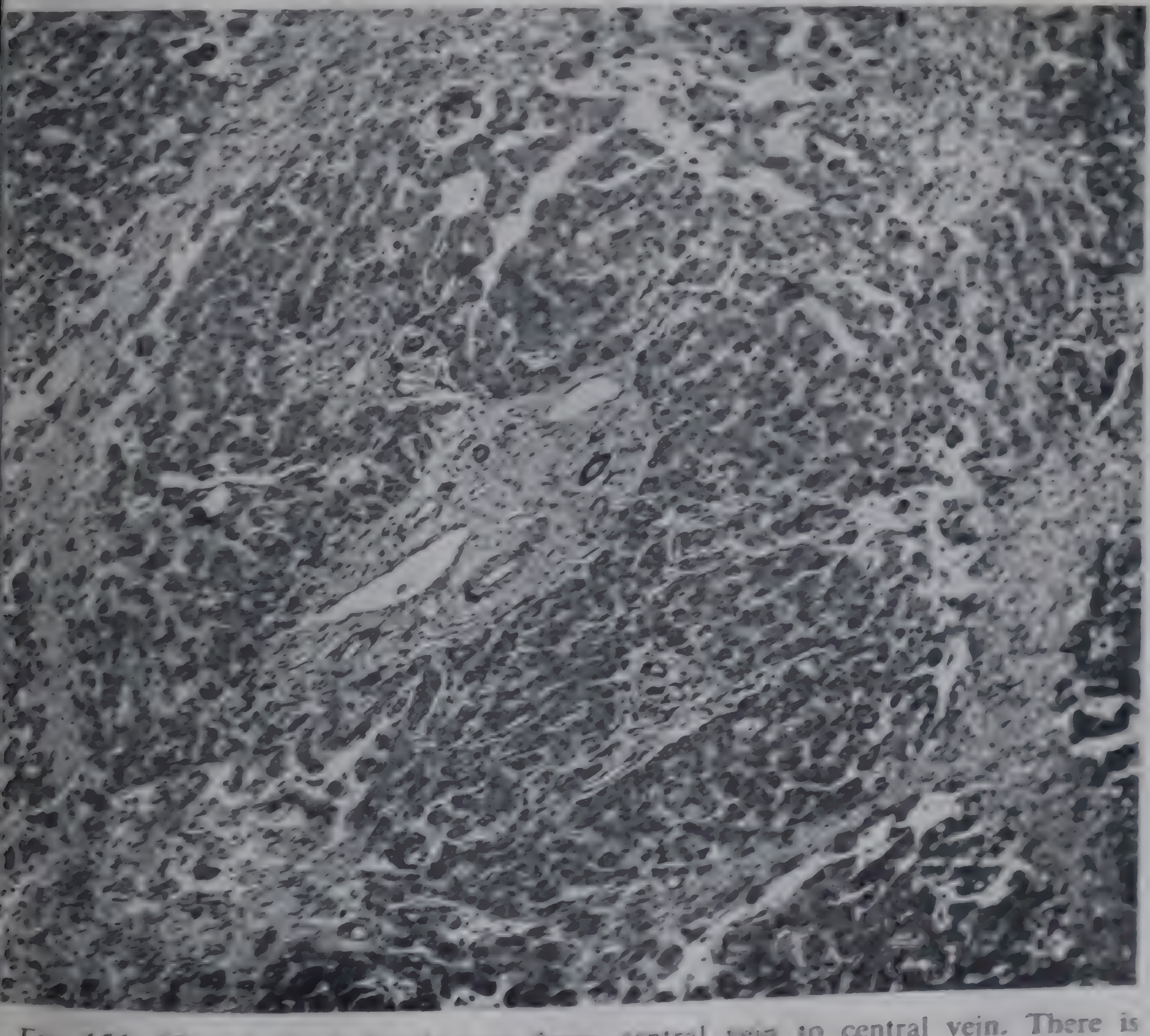


Fig. 156. Fibrous tissue bands pass from central vein to central vein. There is reversed lobulation" and a fully developed cardiac cirrhosis. Portal tracts show only light fibrosis (H.E. × 90)

TABLE 42. HEPATIC RETICULIN CHANGES RELATED TO THE EXTENT OF HEPATIC CELL NECROSIS AND TO THE TYPE OF HEART FAILURE

	RETICULIN PATTERN CHANGES (NO. OF PATIENTS)			
	Normal	*Centrilobular Condensation*	*Centrilobular Proliferation*	*Cardiac Cirrhosis*
Extent of hepatic necrosis:				
Grade 1	16	1	1	0
2	3	2	3	7
3	4	5	2	6
Type of heart failure:				
Primarily valvular mitral	3	2	2	11
Aortic	4	2	0	0
Cor pulmonale	7	1	2	2
Hypertensive	6	1	1	0
Ischemic	3	2	1	0

(Sherlock, S.: The liver in heart failure, relation of anatomical, functional and circulatory changes. Heart J. 12:273)

CLINICAL ASSOCIATIONS (TABLE 42)

Centrizonal hepatic cell necrosis occurs in all forms of heart failure, but the severer grades usually are associated with mitral stenosis or constrictive pericarditis. In general, the longer the patient has been in failure the greater is the extent of the underlying damage to the liver. If failure exists for longer than 60 days, a severe hepatic lesion ca
expected.

Cardiac cirrhosis is most often associ
with mitral stenosis complicated by tricu
valvular incompetence. It is an almost
stant complication of constrictive peri
ditis. However, cardiac cirrhosis can o
with all forms of heart failure, provided

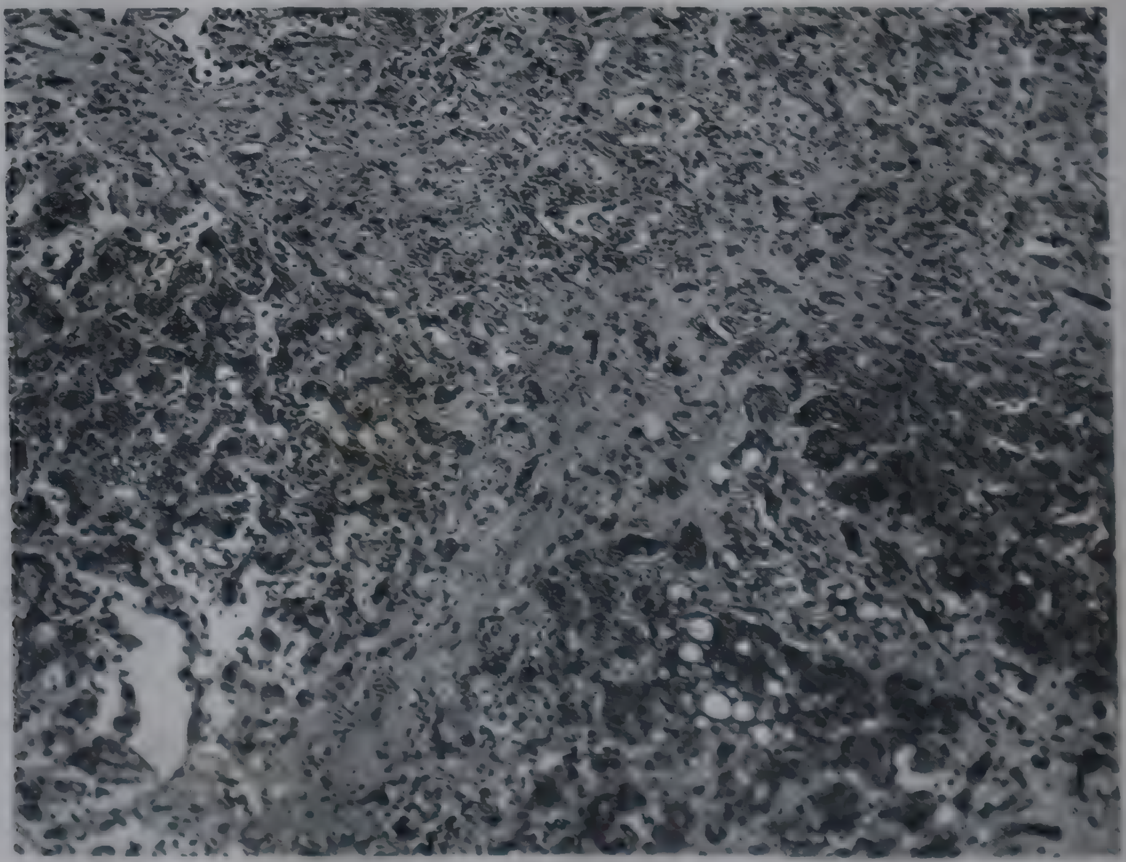


FIG. 157. Postmortem sections show an active cardiac cirrhosis. Portal tracts are also involved, giving a mixed portal and cardiac cirrhosis. (H.E. × 120)

continue for a sufficient length of time at there are repeated episodes of failure. incidence depends on the strictness of histologic criteria adopted for diagnosis. term "cardiac cirrhosis" should be used if there is an alteration in the architec- pattern of the liver as well as fibrosis. nomatous regeneration of liver cells and bile duct formation should be included .[5] With these criteria an instance of 0.4 cent of all autopsies seems to be a reason- one.[28]

MECHANISM AND RESULTS OF THE HEPATIC CHANGES

entrilobular Hepatic Necrosis. The liver articularly sensitive to oxygen lack, and integrity of the liver cell depends on an quate oxygen supply. The liver cells at the ter of the lobule receive blood at a lower gen tension than at the periphery[1] and refore are more susceptible to any fall in oxygen supply to the liver. Anoxia is wn to cause both degeneration of central r cells[24] and dilatation of sinusoids.[45] heterization studies in man have shown t as the cardiac output diminishes, the atic blood flow diminishes in propor- 1.[38] The oxygen supply to the liver de- ases with diminishing cardiac output, and centrilobular hepatic necrosis in heart ure can be related to the degree of de- ssion in cardiac output.

The oxygen supply to the liver depends only on the hepatic blood flow but also the oxygen content of the portal venous hepatic arterial blood. The arterial oxy- saturation in most types of congestive rt failure is reduced only a little, and this tor is of importance only in patients with monary or congenital heart disease having wered arterial oxygen content. The portal ous oxygen level may be reduced in con- tive heart failure, and certainly the hepatic n catheterization studies have shown that hepatic venous oxygen content is lower n normal.[16, 39] The liver cells are perfused a slow rate with poorly oxygenated blood, this must play a part in the genesis of centrilobular necrosis.

The hepatic venous pressure is raised in rt failure, reflecting the rise in pressure the right side of the heart, and this might conduce to the centrilobular necrosis.[39] Severe hepatic necrosis usually is associated with a high hepatic venous pressure, and it is worthy of note that patients with constrictive pericarditis with greatly elevated hepatic venous pressures also have very severe centrilobular necrosis. However, as Bolton[6] pointed out, it is doubtful whether the centrilobular changes produced by passive venous congestion can be purely mechanical, since the rise in pressure must extend from the hepatic vein through the lobule to the portal veins.

In summary, it seems likely that the centrilobular changes in heart failure result from a combination of hepatic anoxia and hemorrhage from distended sinusoids, due to the increase in the venous pressure.

CLINICAL ASPECTS OF CARDIAC CIRRHOSIS

The fibrotic changes in the liver occur secondary to the anoxic centrilobular necrosis and are probably reparative. This central fibrosis then proceeds to a centrilobular cirrhosis. The relative rarity of this condition probably is related to the infrequency of prolonged heart failure. Most patients die in the stage of centrilobular reticulin condensation and never pass to the proliferative regenerative phase. Repeated episodes of failure are necessary for the development of a full cardiac cirrhosis.[27] Patients with rheumatic mitral stenosis, especially with tricuspid valvular incompetence, responding intermittently to treatment, are therefore particularly prone to develop cardiac cirrhosis. If patients with other forms of heart failure survive for a sufficient length of time, they too can develop the same lesion.

Although the connective tissue in heart failure is primarily centrilobular, in the later stages the portal tracts become involved. Fibrous bands link not only central areas but also portal tracts. This may account for the reported frequency of portal cirrhosis in heart failure.[22] If serial hepatic biopsies are taken, however, it is shown that the essential cirrhosis of heart failure is a centrilobular one and that involvement of the portal tracts is merely a later, confusing feature.[50]

Cardiac cirrhosis per se does not seem to have any deleterious effect on the patient. It must be distinguished from the symptom of cardiac jaundice, for patients with cardiac cirrhosis are not more jaundiced than those in heart failure but without hepatic fibrosis. Cardiac cirrhosis does not seem to cause any specific alteration in the serum protein values or the seroflocculation tests of liver function. The centrilobular fibrosis of heart failure does not seem to cause obstruction to the portal venous blood flow. Superficial abdominal veins are not distended, hematemesis does not occur, and esophageal varicosities are not seen at autopsy. The spleen is not larger in patients with cardiac cirrhosis than in those with heart failure but without cirrhosis. It is only in the very severe cardiac cirrhosis associated with constrictive pericarditis that portal hypertension might be considered. The clinical recognition of cardiac cirrhosis usually is impossible.[5, 50] It should be suspected in mitral disease with repeated episodes of heart failure, especially if there is associated tricuspid valvular incompetence or in patients with constrictive pericarditis. Most patients with heart failure and deep jaundice have also cardiac cirrhosis, but most patients in whom cirrhosis is present will give no clinical indications of this lesion, and the diagnosis is a purely academic one, confirmed at autopsy.

If the heart failure is controlled, acute hepatic changes disappear, and the liver shows only avascular fibrous bands passing between central veins. The hepatic cirrhosis is quiescent or latent. This is analogous to the latent cirrhosis sometimes resulting from acute virus hepatitis.[49] This type of cirrhosis is of no clinical significance.

Edematous areas may not be jaundiced. Bile pigment is attached to protein and does not enter the edema fluid because of its low protein content.[37] However, this may not be true, as more recent work has shown no correlation between the bilirubin and the protein content of edema fluid.[29] The jaundice is not associated with pruritus.

The urine is dark and concentrated and shows excess of urobilinogen. If the jaundice is deep, bile pigment may be detected in the urine.[50] The stools are usually darker in color than normal, and fecal stercobilinogen is increased. Occasionally, however, if the patient is very deeply jaundiced, the stools may be gray in color.[20]

CLINICAL EXAMINATION OF THE ABDOMEN IN CONGESTIVE HEART FAILURE

THE LIVER

The patient may complain of spontaneo right abdominal pain, similar to that expe enced in the early stages of acute infecti hepatitis. In both conditions the pain pro ably is due to stretching of nerve endings the capsule of the liver.

The liver usually is enlarged, the low edge often extending to the umbilicus. Th edge is firm, smooth and tender on palpatio Tender enlargement of the liver is an ea sign of congestive heart failure, often pr ceding peripheral edema.

HEPATIC PULSATION

A rise in pressure in the right auricle transmitted readily not only to the neck vei but also to the inferior vena cava and hepatic veins. This transmission of pressu from the right auricle to the hepatic veins particularly conspicuous in tricuspid valvu incompetence when pressure tracings tak from the hepatic veins show a contour simi to those obtained from the right auricle. both there is obliteration of the normal terval between the "c" and "v" waves of phlebogram. The pulsation of the liver wh occurs in tricuspid incompetence can be lated to this transmission of pressure.

The pulsation is palpable and occ during ventricular systole. Its expansile ture may be felt bimanually with one ha over the liver in the right upper quadrant the abdomen and the other over the ri lower ribs posteriorly. This expansibility tinguishes it from the palpable epigast pulsation due to the aorta or to a hyp trophied right ventricle. Very vascular mors sometimes cause the liver to puls but they are very rare. If a cardiac cirrh develops, the pulsation is lost.

THE HEPATOJUGULAR REFLEX

In the patient in heart failure, if press is applied over the liver in the epigastri the large veins of the neck are seen to The hepatic compression increases the nous return and intensifies the distentio the neck veins due to the inability of ng right heart to handle the increased ıd flow. Therefore, the reflex is seen par-larly well in heart failure. It is of value: for the better identification of the upper ls of venous pulsation in the neck; (2) to blish that venous channels between the atic and the jugular veins are patent. refore, the reflex will be negative in ld-Chiari's disease (hepatic venous oc-ion) or with blockage of the main medi-nal or jugular veins.

THE SPLEEN

he spleen may be enlarged and palpable. s may have various explanations and is necessarily indicative of cardiac cirrhosis.

ASCITES

he ascites of heart failure may be related 3 factors: (1) rise in hepatic venous pres-e; (2) change in the plasma protein con-tration; (3) sodium retention.

ise in Venous Pressure. In animals, ex-imental obstruction to the venous return m the liver is a common way of producing ascites. The rise in the hepatic venous pressure in congestive heart failure is probably of similar importance.

Plasma Protein Changes. The plasma proteins tend to be lowered in congestive heart failure due to malnutrition, to the patient's being on a restricted diet and having no appetite, to liver cell destruction with impaired protein synthesis, and to loss of protein into edema and ascites.

Sodium Retention. The patient in congestive heart failure has difficulty in excreting sodium, which is retained in the tissues and holds water with it. Although this may not initiate the fluid retention of heart failure, it is probably of importance in its perpetuation.

Therefore, the patient who develops ascites has a particularly high venous pressure, a low cardiac output and associated, severe, centrilobular liver cell damage. This description can be applied to the patient with mitral stenosis with tricuspid incompetence and to the patient with constrictive pericarditis, and it is with these two conditions that ascites is closely associated. Occasionally, the

TABLE 43. BIOCHEMICAL RESULTS IN 50 PATIENTS WITH HEART FAILURE

ent of patic rosis	Serum bilirubin mg./100 ml.		Serum alk. phosphatase units/100 ml.		Serum albumin g./100 ml.		Serum globulin g./100 ml.		Bromsulphalein percentage retention at 30 minutes	
	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean	No. of Cases	Mean
rmal	—	(0.5–1)	—	(4–13)		(3.4–5.0)	—	(1.5–3.0)	—	(0–10)
ade 1	18	1.1 0.24* (0.5–4.7)†	17	9.3 1.07 (6.0–25.0)	16	4.1 0.10 (3.4–4.7)	16	2.5 0.15 (1.4–3.6)	6	11.3 (2–30)
ade 2	15	2.0 0.33 (0.5–5.0)	15	10.3 1.21 (6.0–20.0)	15	3.5 0.18 (2.2–4.7)	15	2.9 0.17 (1.4–4.2)	7	18.0 (1–48)
ade 3	17	3.3 0.13 (0.9–7.4)	13	12.3 1.03 (4.7–26.0)	12	3.5 0.21 (2.4–5.1)	12	2.9 0.13 (1.6–3.7)	8	24.6 (7–53)
OTAL	50	2.1 0.19 (0.5–7.4)	45	10.5 0.73 (4.7–26.0)	43	3.7 0.11 (2.2–5.1)	43	2.8 0.12 (1.4–4.2)	21	19.0 2.53 (1–53)

* = standard error of mean.

† = range.

Sherlock, S.: The liver in heart failure, relation of anatomical, functional and circulatory changes. Brit. art J. **12**:273) ascites may be out of all proportion to the edema and to the other symptoms of congestive heart failure. Cardiac cirrhosis can be related to ascites only inasmuch as both occur in patients with severe liver cell damage.

PROGNOSIS AND TREATMENT

The prognosis of the liver changes in heart failure are those of the heart disease which caused them. Cardiac jaundice, particularly if deep, is always a bad omen unless associated with a sudden frank pulmonary infarct.

Cardiac cirrhosis per se does not carry a bad prognosis, and if the heart failure responds to treatment, the cirrhosis can be expected to become latent.

Treatment is that of the heart failure. Diet should be adequate in protein, and it must be remembered that the salt-free diet used for the treatment of congestive heart failure may be inadequate in other respects and may need supplementing.

LIVER FUNCTION TESTS (TABLE 43)

Serum Bilirubin Concentration

The serum bilirubin is raised with congestive heart failure, but very high values are unusual.

The level of the serum bilirubin corresponds closely to the degree of clinical heart failure. When this returns to normal the bilirubin returns to normal also. It has been suggested that when cardiac compensation is attained and the total serum bilirubin remains raised, permanent hepatic damage is present.[46] This has not been my experience, and the serum bilirubin may be normal in the presence of cardiac cirrhosis if this is a compensated state.

The van den Bergh reaction is usually indirect, but this is dependent on the degree of bilirubinemia and if gross the reaction becomes direct. It is of no value in diagnosis.

The Bromsulphalein Reaction

This is the most sensitive method of detecting hepatic involvement in the patient with congestive heart failure.[3, 11, 17, 21] It is a pigment overload test and is analogous to the pigment overload when tissue infarction occurs in the patient with congestive hea failure. Results are parallel for both the clin cal severity of failure[16] and the severity the hepatic cell necrosis as shown by b opsy.[50] It has been suggested that the lowere hepatic blood flow in heart failure may con tribute to the abnormal bromsulphalein test The close parallelism between the histolog changes in the liver and results for the bron sulphalein test makes this unlikely.

Also, it has been thought that if the bron sulphalein test remains abnormal after clin cal recovery from the heart failure, there cardiac cirrhosis.[16] This again has not bee my experience.

The *urine* always contains excessi amounts of urobilinogen, and if the patie is deeply jaundiced bilirubin also can detected.[50]

The *serum alkaline phosphatase* conce tration is usually normal.

The *serum total cholesterol* level is usual normal. If the failure is of rheumatic etiolog it may be depressed, perhaps because t illness has been of long duration and is ass ciated with much malnutrition.[17, 40] Patien with arteriosclerotic and hypertensive hea failure may have high serum cholester values, but this probably is related to t vascular disease, rather than to the effects heart failure on the liver.

Serum Protein Levels

Although the mean values for total seru protein, serum albumin and serum globu may be normal, there is much variation in t individual patient. In my series of 43 patie with congestive heart failure, 12 had a seru albumin value less than the normal low limit of 3.4 Gm./100 ml., and 18 patie had a serum globulin level above the upp normal limit of 3 Gm./100 ml. In anoth series, 29 per cent of the patients had a pressed serum albumin.[17] The low ser albumin values occur in the patients w severe hepatic necrosis and must be due part to defective hepatic synthesis of prote They also occur in the patients with the m edema in whom protein, particularly alb min, is lost into edema fluid. With recov from the heart failure the plasma prote return to normal.

SEROFLOCCULATION TESTS

Although the thymol turbidity or floccu-
tion test or cephalin cholesterol test occa-
onally may be positive in congestive heart
ilure,[9, 17] these tests usually give negative
sults.

SUMMARY

Abnormal hepatic function tests in pa-
ents with congestive heart failure are an
dex of the centrilobular hepatic necrosis
nd atrophy of liver cells and cannot be used
s an indication of cardiac cirrhosis or of
ermanent liver cell damage.

CARDIAC JAUNDICE

INCIDENCE

Although overt jaundice is rare, biochemi-
al jaundice as evidenced by a raised serum
ilirubin concentration is a common finding
n congestive heart failure.[11, 21, 28, 44] Of the
0 patients in congestive heart failure which
studied, 34 had serum bilirubin levels
reater than 1 mg./100 ml., and in 16 of
hese the value exceeded 2 mg./100 ml.
Moreover, in 8 of the subjects jaundice was
eep with a serum bilirubin greater than 4.5
ng./100 ml. The 3 highest values were 18.0,
1.5 and 22.0 mg./100 ml. and compare
ith the levels found in mechanical obstruc-
on of the common bile duct.

AUNDICE AND THE CAUSE OF THE HEART FAILURE

Mild degrees of jaundice may occur with
ll the common varieties of heart failure—
alvular, hypertensive, ischemic or pulmo-
ary. Deeper icterus has a closer association
ith valvular heart disease and in particular
ith mitral stenosis, especially if there is an
ssociated tricuspid valvular incompetence.
he incidence increases with prolonged con-
estive heart failure, and repeated bouts also
ontribute to the incidence.[5]

CLINICAL FEATURES OF THE JAUNDICE

The jaundice is usually mild and of a
mon-yellow color, although in occasional
atients it may be deep and greenish, simu-
ting obstructive jaundice.

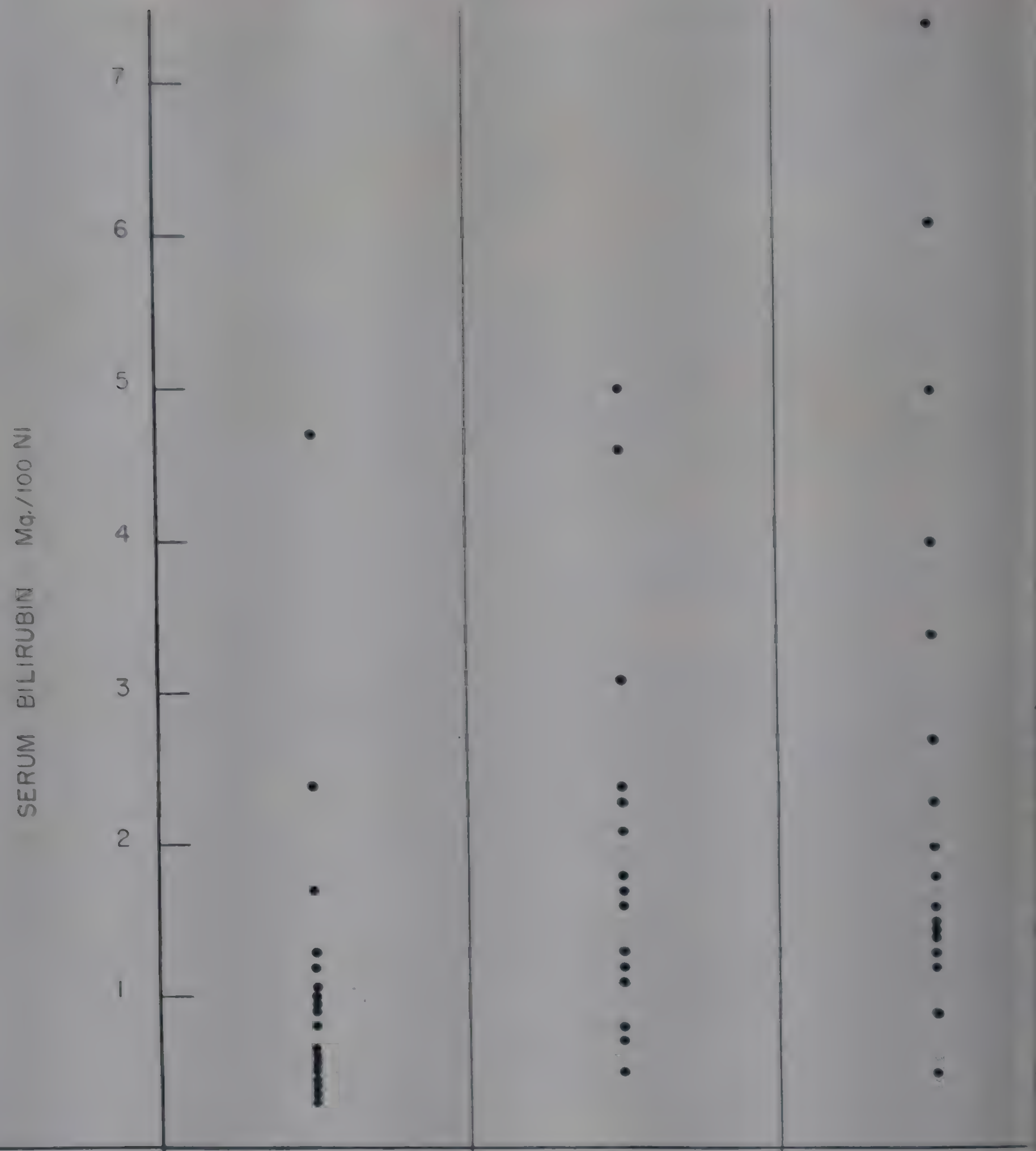
ETIOLOGY

Hepatogenous Jaundice. This implies that in heart failure the liver cells are inadequate to excrete all the bile pigment. The impaired liver function tests are in keeping with this concept, and in general the greater the extent of liver cell necrosis the deeper the icterus (Fig. 158). There are many exceptions to this rule, however, and in particular the occurrence of tricuspid incompetence with severe liver damage but without clinical icterus. Liver cell damage cannot entirely explain cardiac jaundice.

Obstructive Mechanical Jaundice. Eppinger[15] believed that cardiac jaundice was due to obstruction of bile capillaries, both by pressure on the outside by distended veins and by inspissated bile thrombi within. The obstruction may be related to the height of the venous pressure within the hepatic lobule. The normal biliary secretory pressure is 20 to 30 cm. water.[31] Many patients with heart failure have right auricular pressures of 20 cm. saline. The hepatic venous pressure has been shown to be higher than this and may be greater than the pressure at which bile can be secreted.[16, 39] A mechanical obstruction to the intralobular bile canaliculi might exist. Moreover, patients with deep jaundice often have very high right auricular pressures, and a statistical correlation may be established between the depth of jaundice and the venous filling pressure of the right heart.[50] The usually close association of tricuspid valvular incompetence (with presumably high hepatic venous pressures) and deep jaundice has been noted already.

Inspissation of bile in the minute canaliculi to form "bile thrombi" is commonly evidence of biliary obstruction. Bile thrombi are conspicuous in the livers of patients with deep cardiac jaundice but are seen in every condition where jaundice is deep, and particularly when the bile is viscid, as in hemolytic crises. Therefore, their presence is not necessarily indicative of biliary obstruction. In addition, the centrilobular destruction of liver cells and hemorrhage in heart failure may disorganize the bile canaliculi and produce stagnation of bile and hence thrombi.

Other evidence against the hepatic venous-obstructive theory of cardiac jaundice may



Histological grade	A	B	C
Mean serum bilirubin mg./100 nl.	1.1	2.0	3.3
Number of patients	18	15	17

FIG. 158. The relationship of extent of hepatic necrosis to the serum bilirubin concentration. (Sherlock, S.: The liver in heart failure, Brit. Heart J. 13:273)

be given. The relationship between high venous pressure and jaundice is not constant, and some patients with tricuspid incompetence and very high hepatic venous pressures are not jaundiced. At autopsy the gallbladder and the bile passages, in even those most deeply jaundiced, are full of dark bile, and with very rare exceptions the feces are darker than normal and not suggestive of biliary obstruction. Further, the biochemical dat unlike those of biliary obstruction. S alkaline phosphatase is normal, as ar blood cholates.[31] Urobilinogen is prese excess in the urine. Intrahepatic biliar struction related to high venous pressu therefore unlikely to be an important of cardiac jaundice.

It is doubtful whether bile thrombi

TABLE 44. THE RELATION OF SERUM BILIRUBIN CONCENTRATION AND PULMONARY INFARCTION

f ts	Mean serum bilirubin	Histology of Liver Grade 1 No.	Grade 1 Serum bilirubin (mean)	Grade 2 No.	Grade 2 Serum bilirubin (mean)	Grade 3 No.	Grade 3 Serum bilirubin (mean)	Type of Heart Failure (No. of Cases) Mitral valvular	Aortic valvular	Cor pulmonale	Hypertensive	Ischemic
out pulmonary infarction												
	1.4	11	0.9	10	1.6	7	2.1	7	2	11	4	4
pulmonary infarction												
	3.2	3	2.6	4	3.1	7	3.5	9	2	1	2	0

erlock, S.: The liver in heart failure, relation of anatomical, functional and circulatory changes. Brit J. 12:273)

ver result in clinical jaundice, for they are present in sufficient amounts so significant numbers of bile channels are ed.

molytic Jaundice. The icterus of heart e is often related to hemorrhages into ssue, particularly pulmonary infarctions. udden appearance of jaundice following linical features of an infarct, whether onary, splenic or renal, in a patient with estive heart failure is well recognized.[22] ar infarcts in patients without heart fail- do not result in jaundice.[28] The hemo- n in the infarcted tissues becomes ged to bilirubin, and it is postulated that xcess of pigment so produced cannot be ted by a liver damaged by heart failure, jaundice therefore results.

here are many points in favor of this thesis. There is an excess of iron pig- in the tissues in heart failure, and con- on, particularly in the lungs, may be more important than frank infarction. without frank infarcts the pulmonary li usually contain "heart failure" cells. e macrophages show iron pigment, pre- bly derived from red blood corpuscles. ubin also must have been formed, con- ing an additional excretory load on the Although there are exceptions, patients pulmonary infarction show a higher n bilirubin level than those without le 44). In one reported series of 424 sies on patients in heart failure, jaun- was noted in 4 per cent of the whole , but in 10.5 per cent of those with infarcts.[28] In some patients jaundice develops after infarction, although the right auricular pressure and the cardiac output are not changed, and liver biopsy shows only minimal histologic changes. In these patients jaundice can be associated only with infarction. Patients with minimal liver cell damage in heart failure who become jaundiced usually have clear evidence of pulmonary infarcts.[50] Biochemical results support a hemolytic etiology. The stools are dark,[18] the urine contains excess urobilin, and blood biochemical findings are compatible.

At the same time, pigment overload cannot be the only cause of cardiac jaundice. Rich and Resnik[43] introduced into the tissues of patients with heart failure a volume of blood equal to that found in pulmonary infarctions and failed to increase the serum bilirubin level. Although bilirubinuria is not found in hemolytic icterus, it is often found in patients with cardiac jaundice, and occasionally the stools are pale. Finally, jaundice may occur without pulmonary infarction and may be particularly conspicuous in association with tricuspid incompetence in which pulmonary vascular congestion is minimal.

SUMMARY

Cardiac jaundice is very complex. Support can be found for hepatocellular, obstructive and hemolytic theories. In most patients multiple factors are present, the most important being hepatocellular anoxia and increased pigment overload of the liver cells, resulting from the liberation of blood into the tissues.

THE LIVER IN CONSTRICTIVE PERICARDITIS

Hepatic changes are particularly severe but are essentially similar in pattern to those described in patients with right-sided congestive heart failure.

Macroscopically, if the constriction has been prolonged there is usually a cardiac cirrhosis. The capsule of the liver is greatly thickened and has been likened to that of sugar icing (*Zuckergussleber*).

Microscopically, the picture is of centrilobular cardiac congestion and necrosis, progressing to a mixed portal and cardiac type of cirrhosis. Portal zone connective tissue and new bile duct formation may be particularly prominent.[26]

CLINICAL FEATURES

The patient is not jaundiced. The liver is enlarged, and the edge is hard; it does not pulsate. The spleen is usually palpable. Ascites is prominent, and the resultant dyspnea and abdominal swelling may be the main complaints. Peripheral edema may or may not accompany the ascites. The mechanism of the ascites has been discussed already.

There may be considerable difficulty in distinguishing constrictive pericarditis from chronic hepatocellular failure with ascites. In both, the jugular venous pressure in the neck is raised, although it is usually higher with constrictive pericarditis. The diagnosis is made by the paradoxical pulse, the radiologic demonstration of calcium in the pericardiu and the characteristic electrocardiogram.

BIOCHEMICAL FINDINGS

Biochemical findings include a serum bil rubin level rarely higher than 2 mg./100 m a positive bromsulphalein retention test ar altered serum proteins with a level album and a high globulin value. The seroflocul tion tests are usually normal but occasionall in longstanding cases, may be positive.

TREATMENT

Treatment is that of the cardiac conditio If pericardectomy is possible, prognosis regards the liver is good, although recove may be slow. Within 6 months of a succes ful operation, liver function tests will i prove, and liver size will shrink.[33] The ca diac cirrhosis cannot be expected to resol completely, but the fibrous bands in the liv become narrower and avascular, and it i doubtful if they then cause clinical sympton

If the pericardial lesion is inoperable, t treatment is that of any cirrhosis with ascit namely, sodium restriction, with salt-free etary protein supplements.

THE LIVER IN BACTERIAL ENDOCARDITIS

The liver may show focal necrosis of li cells with surrounding polymorphonucl infiltration, presumably embolic in natu Congestive changes may occur if the pati is in heart failure but are unusual, and c diac cirrhosis is rare.

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hapter 20

SYPHILIS OF THE LIVER

Franklin M. Hanger, M.D.

Many misconceptions regarding syphilis the liver have been advanced from time to me and incorporated into medical tradition. he subject has been complicated by the un- itical practice of ascribing to the *Trepo- ema pallidum* or to the toxic effects of erapy all types of hepatic abnormalities de- eloped by the luetic patient. Further con- sion has arisen because the clinical features syphilis of the liver are highly variable and ay be indistinguishable during life from un- lated entities such as Laennec's cirrhosis, ute and chronic hepatitis, primary disorders the collagen system, neoplastic infiltration granuloma from other causes.

INCIDENCE

Specific involvement of the liver occurs in out 5 per cent of inadequately treated philitics. Gross lesions were observed in out 4.5 instances per 1,000 routine autop- es in Hahn's series[2] collected before 1941. t present, with better clinical management, philis of the liver is truly a medical rarity. about one half of all cases with hepatic in- lvement, lesions in other organs such as the ntral nervous system, the testes, the skin d especially the cardiovascular system are monstrable.[4] The coexistence of tabes dor- lis is notably infrequent. The disease may encountered during all ages from early ult life to advanced senescence. Race and are not important conditioning factors.

PATHOLOGY

The intense infestation of the liver with the *eponema pallidum* in the stillborn fetus d in infants dying of congenital syphilis resents an overwhelming spirochetemia rather than a hepatopathy and needs no special discussion.

Hepatic involvement during the course of secondary syphilis is suggested by the common occurrence of diffuse hepatic tenderness and enlargement, impaired bromsulphalein excretion and depression of other functional tests, presence of a positive cephalin flocculation reaction and, rarely, mild jaundice. Hepatic dysfunction is seldom debilitating and is never fatal. The condition reverts to normal promptly with antiluetic therapy or gradually with subsidence of the hyperimmune state. Histologic studies of the hepatic lesions in secondary syphilis are meager but are said to consist of small intra-acinar granulomata and diffuse inflammatory changes in the reticuloendothelial structures. Gummata or necrotizing lesions of the parenchyma are notably absent.

The intrinsic lesion of tertiary syphilis of the liver is the syphiloma which is a macroscopic, confluent, granulomatous process destroying en masse by ischemia and necrosis all hepatic structures in the involved area. Syphilitic endarteritis is no doubt an important factor in the development of the lesion and in the causation of the central necrosis, which characterizes the gumma. Gummata have a tendency to be multiple, to develop at random and to heal spontaneously with radiating contractile-scar formation. This process over the course of months and years gives rise to the classical lobulated, botryoid deformity or the hepar lobatum. The degree of hepatic involvement varies widely and may consist merely of inconspicuous scars on the surface or in the substance of the liver. In other instances, lesions in all stages from fresh syphilomata to healed gummata may be demonstrable. As will be indicated, the clinical picture is determined largely by the location as well as by the extent and the activity of the disease process, and there is little justification for the arbitrary classifications of the disorder proposed by various authors.

The liver is seldom notably enlarged unless chronic passive congestion or cirrhosis is also present. Contrary to a general impression, the left lobe is not conspicuously hypertrophied. Moderate enlargement of the spleen occurs in about 15 per cent of cases, especially in those with portal hypertension. In rare instances, splenomegaly with features of hypersplenism may be present. Thrombosis of the portal vein is an uncommon complication. Scarring and nodulation of the liver may cause pressure on the inferior vena cava and the ostia of the hepatic veins, giving rise to collateral veins over the abdomen, ascites, dependent edema and disturbed electrolyte and water retention by increased pressure in the renal veins. Syphilis is one of the causes of the Chiari syndrome.

Despite the claims of many observers, it is doubtful if syphilis ever gives rise to diffuse scarring such as is seen in Laennec's cirrhosis or chronic idiopathic hepatitis. Both processes may occur in the same liver (1%), since many untreated luetics are alcoholics and irregular in dietary habits, but the association is probably coincidental despite the general clinical impression that the course of hepatitis and cirrhosis is often more severe and unremitting in those who have had syphilis or those who have received extensive arsenical therapy. Hepatomas, which not infrequently complicate Laennec's cirrhosis, are not found in hepar lobatum.

Conspicuous hepatic derangements may follow antiluetic therapy, especially when arsenicals are employed. Many of the cases of intense jaundice and massive necrosis of the parenchyma developing 3 weeks or longer after medication now are recognized in retrospect to be instances of viral hepatitis transmitted by the use of syringes or medical equipment contaminated with the infecting agent. Other cases of postarsphenamine jaundice have been attributed to the toxic action of arsenicals when the arsphenamine retained in the liver is transformed to hepatotoxic derivatives.[1] These cases of delayed postarsphenamine reactions are indistinguishabl clinically from viral hepatitis.

A third type of hepatic derangement foun in arsphenamine therapy is the developmer of a diffuse cholangiolitis due apparently a sensitization of the smaller biliary radicl to arsenicals. The cases are characterized b history, laboratory findings and histolog lesions.[8] The first injection of arsphenamin is usually uneventful, but subsequent inje tions are followed within a few hours by m laise, fever, abdominal pain with the develo ment of jaundice, itching and light stool The cephalin flocculation reaction remai negative, but there is gradual rise of seru alkaline phosphatase and serum cholester Biopsy of the liver shows normal hepatic p renchyma with evidence of intrahepatic bi ary obstruction. The portal triads are edem tous and infiltrated with inflammatory cel The condition subsides gradually with special therapy.

CLINICAL FEATURES

The majority of instances of syphilis of liver have no symptoms or signs suggest hepatic disease. Pain in the right upper qu rant, epigastrium or referred to the back curs in about one sixth of the recogni cases, especially when lesions involve serous surfaces. The pain usually consists a dull ache, which is seldom aggravated breathing and rarely is of the intensity suggest an acute abdominal condition. I relieved promptly by antiluetic therapy.

Protracted or intermittent low-grade f is rare in most case reports. Its prese probably reflects active inflammatory ph of the disease. There may be also in s cases abdominal swelling, loss of weight, sodes of mild jaundice, indigestion, anor constipation or diarrhea, but none of t symptoms is constant or of specific diagn value.

Often the physical examination is also revealing. In only about 10 per cent of is the liver found notably enlarged or ter or can abnormal lobulation be detecte palpation. Syphilis of the liver usually a benign course and is not incompa with longevity. However, about one thi

lected cases eventually die of the disease.
struction of hepatic parenchyma usually
es place so gradually that hepatic insuffi-
ncy seldom develops due to gummatous
lacement. However, when constricting le-
ns involve the porta hepatis, the blood
pply to large portions of the organ may be
off, and massive ischemic necrosis de-
lops rapidly with ascites, deep jaundice,
ma and death. The jaundice in these cases
not of the obstructive type, since gumma-
us lesions rarely cause occlusion of the
ger bile ducts. The most common cause of
ath is hemorrhage. Over 75 per cent of all
alities due to syphilis of the liver result
m portal hypertension with rupture of di-
ed collaterals of the portal vein.

LABORATORY FINDINGS

Since the clinical course is determined
ore by the location of the gummatous le-
on than by the size or the extent of the
ocess, it is obvious that the functional de-
ngements of the liver are also inconstant.
positive serologic test for syphilis is pres-
t in practically all cases with active lesions
t may be negative in treated cases with
ntractile scarring, causing symptoms.

Hyperbilirubinemia is demonstrable in
out one tenth of cases and may reflect ac-
e parenchymal damage or an obstruction
the smaller bile channels. Jaundice is usu-
y mild, except in massive terminal is-
emic necrosis. Bromsulphalein retention is
tably high in this same group of patients.
e cephalin flocculation reaction is usually
gative but may become positive when dif-
se inflammatory lesions or massive necrosis
velop. An elevated serum alkaline phos-
atase determination is of particular value
detecting deforming syphilitic lesions of
e liver and may be the only abnormal lab-
atory finding in many cases of hepar loba-
m. The serum proteins are often normal,
t a lowering of serum albumin below 3
n. per 100 ml. denotes extensive liver dam-
e. Serum globulin is seldom elevated
ove 3 Gm. per 100 ml. A reversal of the
umin globulin ratio is much more com-
on in cirrhosis or chronic hepatitis than in
hilis of the liver.

DIAGNOSIS

Syphilis of the liver, despite its rarity, should be suspected in all patients with positive serology or with stigmata of syphilis who develop ascites, dilated abdominal veins, hematemesis, mild jaundice or a firm irregular liver. The distinction between this condition and various forms of cirrhosis or neoplastic infiltration may be especially difficult. Indeed, most cases of hepatic disease in luetics eventually prove to be nonsyphilitic in nature. Elevation of serum alkaline phosphatase, relatively normal serum protein patterns and a negative cephalin flocculation reaction may be of assistance in differentiating a syphilitic process from active cirrhosis. Spider angiomata are extremely uncommon in syphilis of the liver. Needle biopsy may be helpful in differentiating the two conditions, since diffuse scarring seldom is caused by syphilis. In one instance of hepar lobatum observed by the author the biopsy specimen consisted entirely of a dense bit of connective tissue, but endarteritis of several of the smaller arteries was of diagnostic value.

The diagnostic importance generally ascribed to the therapeutic test is not entirely justified. Gummata often recede slowly, despite vigorous treatment, and the scar tissue causing symptoms may be regarded as irreversible deformities. Nevertheless, the test is indicated in all doubtful cases, for fever, local tenderness and acute swellings usually respond promptly to iodides and penicillin therapy. The failure of an expanding lesion to decrease in size on an adequate therapeutic regimen is strong evidence for a neoplastic process or some nonsyphilitic infection.

TREATMENT

Syphilis of the liver in all stages warrants prolonged courses of iodides and penicillin, although many cases with constricting deformities are not benefited. Patients with portal hypertension, dilated esophageal varices or massive gastro-intestinal bleeding are grave medical risks, and little is to be gained by prolonged attempts to correct the disorder with antiluetic drugs. Surgical shunting of the portal vein, despite the operative risk, should be urged strongly in these cases.

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Chapter 21

TUMORS OF THE LIVER

Edward A. Gall, M.D.

Hepatic neoplasms are relatively insusceptible to therapeutic attack. Their recognition is nonetheless of salient importance in determining the desirability of surgical exploration, in the selection of a suitable form of therapy, and in the establishment of a prognostic outlook. The need for a clearer distinction clinically between lesions of primary and secondary nature requires no elaboration; examination of vital statistics pertaining to causes of death reveals an obviously impossible recorded frequency of "carcinoma of the liver." Clinical recognition is not a simple matter, however, and tumors of the liver often represent unexpected observations at necropsy. In the case of the benign lesion this is attributable to the relatively small size of the tumor or to the slow rate of growth which evokes few or no symptoms. On the other hand, malignant lesions often escape detection by reason of the obscuring manifestations of such underlying disorders as cirrhosis or primary extrahepatic carcinoma. Moreover, the enormous reserve capacity of the liver permits wide replacement with little perceptible interference with function. Obviously, any improvement in clinical recognition would require an increased awareness and anticipation of liver neoplasm, an understanding of the miscellaneous clinical and laboratory phenomena which may herald these lesions and the development of newer diagnostic methods.

As a basis for discussion the following outline represents a working classification which will serve as an outline for the subject matter of this chapter. It has the doubtful advantage of avoiding definitive but controversial terminology.

1. Primary epithelial neoplasm
    A. Parenchymal
    B. Ductal
    C. Combined (parenchymal and ductal)
2. Endothelial neoplasm
3. Hematopoietic neoplasm
4. Supporting-tissue neoplasm
5. Teratoid and embryonal neoplasm
6. Miscellaneous and uncertain neoplasm
7. Metastatic neoplasm
8. Pseudoneoplasm

PRIMARY EPITHELIAL NEOPLASM

Terminology

A distinction between primary and secondary carcinoma of the liver has been recognized for at least a century.[120] Kelsch and Kiener[65] in 1876 delineated a tumor of hepatic-cell origin, but a recognition of two types of derivation—parenchymal and ductal—was not accomplished until 1911, by Yamagiwa.[126] The term "hepatoma" was proposed initially by Monier-Vinard in 1910.[83] It was intended to designate a benign tumor of hepatic-cell origin in contradistinction to the then nondescript "adenoma" and multinodular hyperplasia.[111] In due course, the term "cholangioma" was introduced to represent the tumor arising from biliary ductular epithelium separating it from the parenchymal-cell lesion.[47] In 1888 Hanot and Gilbert devised a descriptive gross classification (massive, nodular and diffuse) which continues to have wide usage.[55]

Incidence

Primary liver carcinoma has an infrequent occurrence. It is said to appear in 1 in 400 (0.25%) autopsy examinations with a recorded incidence range of 0.02 to 1.05 per cent.[15, 50, 53, 60, 73, 74, 101, 112, 122, 124] The latter figure (1:100) reflects a greater frequency in certain portions of Africa and the Orient (0.74 to 1.05%).[15, 60, 73] It is claimed that the rate is considerably higher in the colored races, but this apparently holds only in their native habitat. The Negro in Africa suffers a much higher incidence of liver cancer than the American Negro, whose rate parallels that of the Caucasian in the same area.[124]

In the selected population of individuals with malignant neoplasm, cancer of the liver comprises 1.5 per cent of the tumors encountered.[15, 25, 88, 112, 122, 124] Among patients with cirrhosis of the liver, a condition considered to be an important precursor of liver neoplasm, the rate of incidence in fatal cases is 1:25 (3.5 to 4.5%).[14, 73, 110] It occurs with at least twice this frequency in hemochromatosis.[14, 101, 110, 122]

Carcinoma of the liver is of more frequent occurrence in males.[50, 60, 122] A ratio of 6:1 is said to be the rate in the case of hepatoma[73] and 2:1 in cholangioma.[50] As Gustafson has indicated, these ratios require adjustment in view of the disproportionately higher number of autopsies carried out in males.[53] It is his contention that the preponderance of men with hepatoma is more properly 2:1, and that with cholangioma the incidence is actually greater in women. In the Cincinnati General Hospital, where the usual male-female postmortem rate obtains, the corrected incidence of cholangioma is 1:1; with hepatoma males predominate, 4:1.[43]

Onset is usual in the sixth decade, the average age given being 55 years.[73] In our own series of 75 cases the average age is 63 years, with negligible difference between the 2 major types. However, it is claimed by some that cholangioma appears at a somewhat older age.[38] Despite a prevalence in middle and old age, there are many cases recorded in children, infants and even in the newborn.[29, 66, 86, 91, 114]

ETIOLOGY

The essential cause of hepatic neoplasm is not known. Many possible precipitating causes have been suggested, but the mo common underlying state is that resulti from tissue injury, necrosis and repair. Th is certainly the case with hepatoma, in whi cirrhosis so often precedes the inception neoplasm.[23, 27] Such factors as the reactiv tion of growth potential in congenital rest and the disturbance of growth characteristi as the result of anomalies of vascular su ply[116] are proposed repeatedly but probab have little importance. The contributory i fluence attributed to parasitic disease,[15, 56, 60, 92] syphilis,[53, 102] nutritional deficiency, alcoholism and hepatotoxic substances,[15, 87, 122] all of which are included also amo the causes of cirrhosis, lend some creden to the concept that many neoplasms of th variety reflect cytologic aberration sup vening upon repair and regeneration. In t Cincinnati General Hospital series evalu tion of the type of cirrhosis indicates th the postnecrotic and posthepatitic variet predominate.

Some 75 per cent of cases of hepato appear in association with pre-existing c rhosis.[14, 38, 124] The range given in the lite ture is 39 to 87 per cent.[73, 124] Nor does fact that the bulk of the liver appeared be normal necessarily indicate that a giv hepatoma arose de novo in a complet normal nidus.[10, 24, 30, 70] In our own mater there were 15 cases in which hepatoma w unaccompanied by cirrhosis, but in at le 4 of these the tumor appeared to arise i sharply localized area of scarring, simulat postnecrotic cirrhosis. Diffuse cirrhosis n not be the only stigma of prior cellu damage in the liver.

COINCIDENTAL DISEASE

The coincidence of cirrhosis with chol gioma is considerably less and generally given as 50 per cent, with a reported ra of 18 to 57 per cent.[42, 60, 73, 122] An uncrit assumption that the type of cirrhosis her similar to that observed in hepatoma thus precedes the neoplasm has led to a r conception of cause-and-effect relations In 12 of our 22 cases with cholangio cirrhosis was also present.[43] In 5 of th however, this was of the biliary variety did not antecede the tumor but followe a direct result of the obstruction produ by it. Hence, in this particular series, although the coexistence of tumor and cirrhosis occurred in 60 per cent, there is evidence hat the cirrhosis pre-existed in only 35 per ent. On the other hand, there is indeed a background of obstruction or chronic bile duct inflammatory disease with some degree of frequency in cases of cholangioma.[38, 102, 126] The potentiality of this mechanism has support in the experiments of Stewart, Canta-ow and Morgan, who observed the appearance of intraductal tumorlike overgrowth following the ligation of single, major bile ducts in the cat.[115] Clinical experience has provided a parallel to this in the significant number of cases in which extrahepatic bile duct carcinoma has been noted in individuals with long-standing biliary tract disease (calculus, stricture).[102] In point also is the high degree of coincidence of gallbladder carcinoma and cholelithiasis. The mucosal epi-

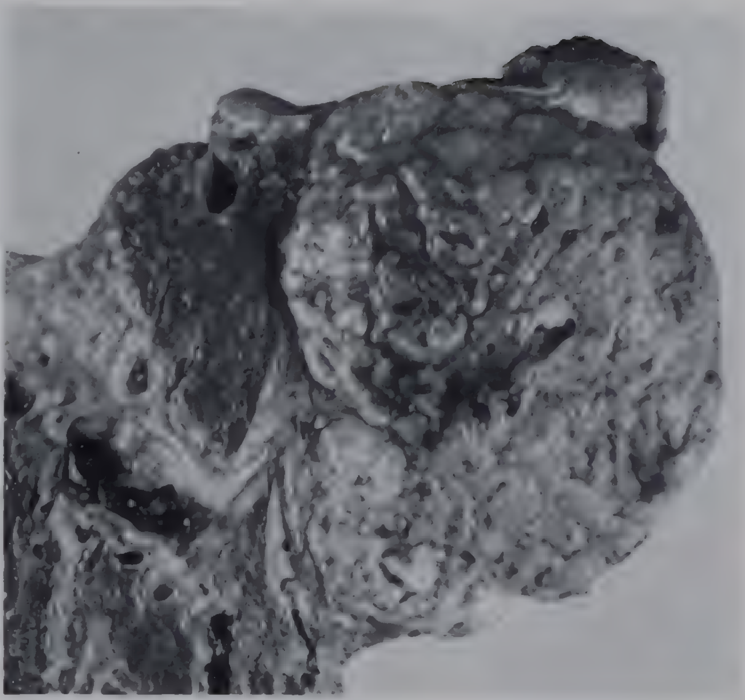


FIG. 159. Hepatoma, massive form. The entire left lobe of a cirrhotic liver has been replaced by a single neoplasm.

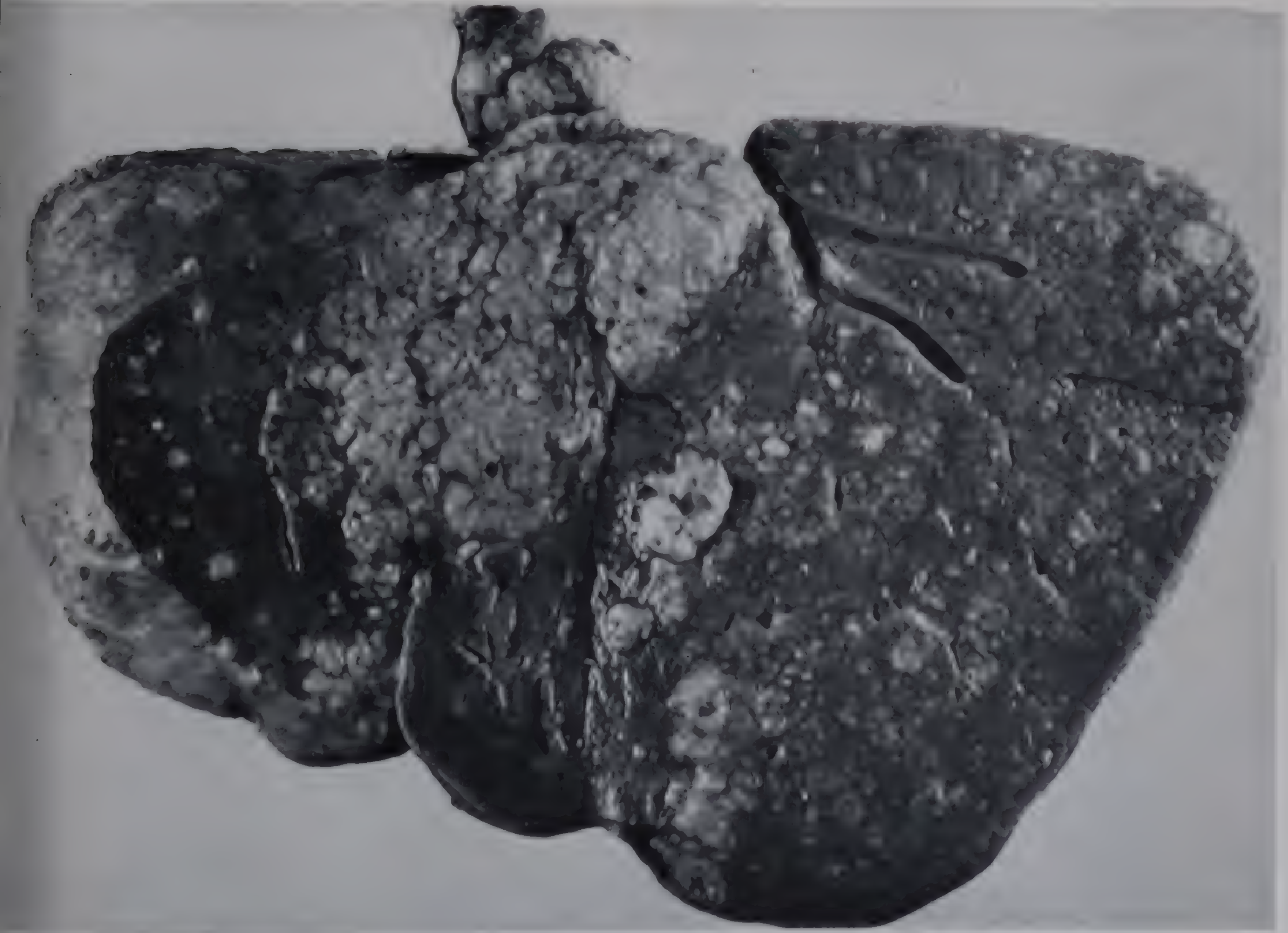


FIG. 160. Hepatoma, nodular form. A major mass abuts upon the upper border of a cirrhotic liver. There are clusters of smaller nodules distributed throughout the remainder of the organ. The tongue of neoplasm projecting above represents an extension into the vena cava via the hepatic vein.

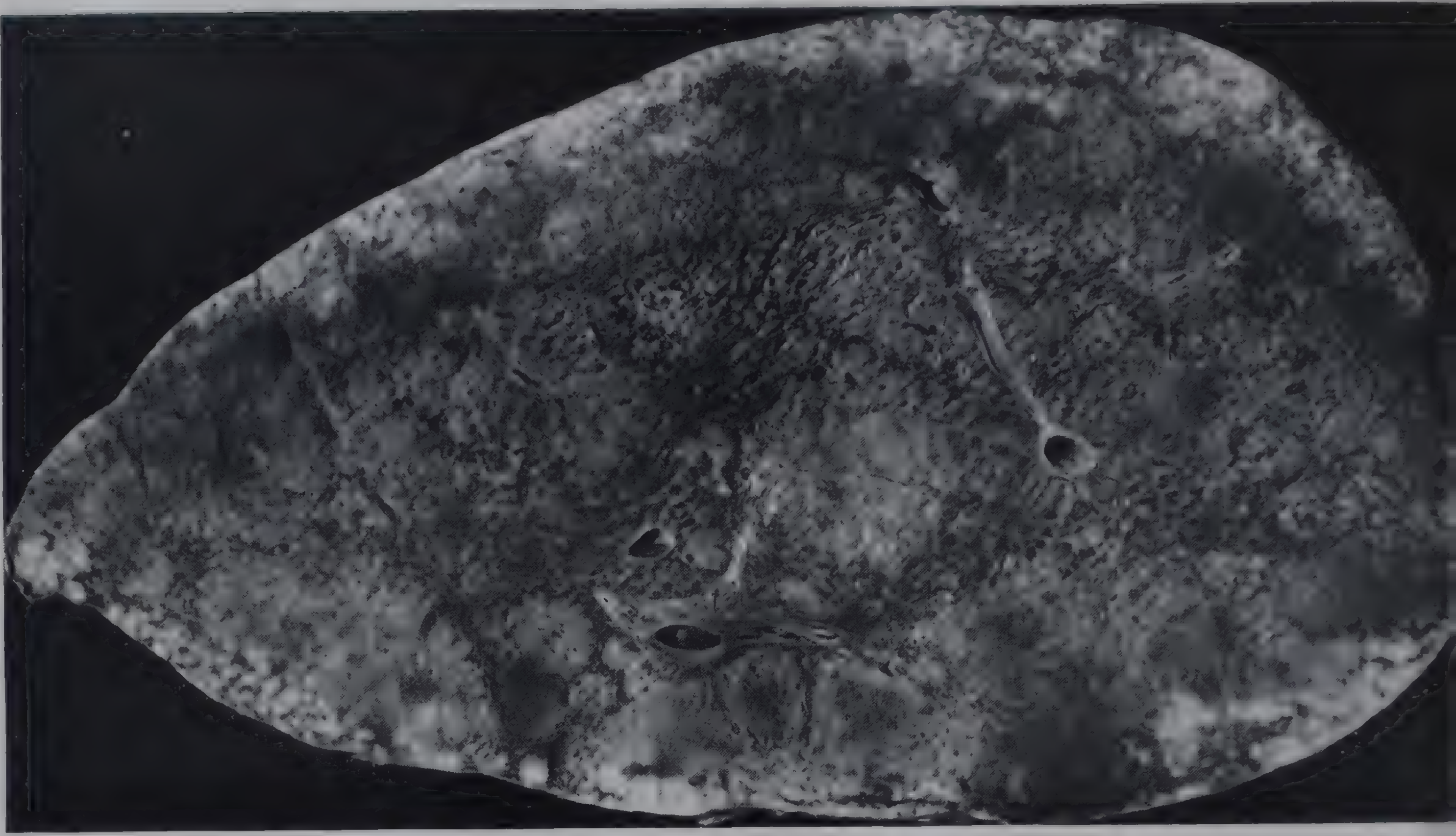


FIG. 161. Hepatoma, diffuse form. A transverse section of the liver, exhibiting diffuse neoplastic replacement of the parenchyma. Circumscribed nodulation is not apparent.

thelium of the bile ducts, both intrahepatic and extrahepatic, and of the gallbladder is histologically indistinguishable.

A large body of literature is devoted to the induction of hepatic tumors in experimental animals. Spontaneous hepatomas have been observed in the cat, the dog and the frog.[84, 124] They occur but are said to be rare in cattle and sheep.[39] Older mice and rats develop them not infrequently.[22, 49] It has been the latter animals in which experimental methods have resulted in a very strikingly increased incidence. Here, even more than in the human subject, cell injury and regeneration appear to provide the basis for abnormal growth release. Although dietary deficiency alone may be effective, the yield of liver carcinoma following the use of a variety of hepatotoxic substances is of very high order indeed. Among the toxic agents used are *p*-dimethylaminoazobenzene (butter yellow),[34, 87, 121, 122] *o*-aminoazotoluene (a scarlet-red derivative),[3, 4, 125, 127] 2-amino-5-azotoluene (another aniline dye)[36] and carbon tetrachloride.[32, 33] Some of the rat tumors produced in this fashion have proved to be transplantable, but this has not
been accomplished with their human cou
terparts.

GROSS PATHOLOGY

Parenchymal Neoplasm (Hepatoma).
has become customary to subclassify tl
tumor into the gross categories propos
by Hanot and Gilbert.[53, 55] Such a divisi
does not imply any biologic distinction, a
there is much overlapping in actual fact.

A *massive* form is characterized by
single large tumor with smaller nodules oft
distributed at its periphery (Fig. 159). T
lesion may attain such proportions as
replace much or all of a major lobe a
displace adjacent structures (stomach, k
ney, spleen, diaphragm). A *nodular* form
manifested by multiple discrete nodules, o
or more of which are larger than the
mainder but never reach the bulk attain
in the massive type (Fig. 160). The less
nodules may appear in satellite fashion
they may be distributed widely through
the liver. The arrangement has given rise
debate as to whether or not this was
result of intrahepatic dissemination from
single source or a manifestation of multi

sites of origin. The third manner of growth, a *diffuse* form, exhibits no discrete tumor formation (Fig. 161). There is wide and noncircumscribed extension throughout the liver with replacement of much of the parenchyma. The process has been referred to as "carcinomatous cirrhosis," a term considered unsuitable, since the prerequisites to cirrhosis do not obtain.[35] This nomenclature should be utilized simply as a convenient means of description; there is no connotation of specificity of action.

The size attained by these tumors is a reflection of the reserve capacity of the liver and the malleability of contiguous viscera. Accordingly, early recognition is rare, and large tumors are the rule. A dearth of stroma is a characteristic of hepatoma; hence, this tumor is considerably softer than other forms of carcinoma. Bile formation is a common feature but it is rarely of a degree to impart a characteristic hue to the neoplasm. Color, indeed, is usually nondescript. A rich vascular component may result in a relatively soft, occasionally pulsatile, purplish red mass which has been mistaken for a hemangioma.[38, 71] Seepage of blood and even massive intraperitoneal hemorrhage occur with a fair degree of frequency.[94, 122]

Venous intrusion is a prominent feature in hepatoma; either the portal or hepatic vein may contain tumor thrombus.[38] This phenomenon serves as the basis for intrahepatic metastasis.[74] It may lead also to progression into the vena cava,[51] or into the main trunk of the portal vein or its tributaries (Fig. 162). As with renal-cell carcinoma, caval propagation of hepatoma may proceed into the right atrial cavity.[38] Spontaneous non-neoplastic portal vein thrombosis is also an important complication.[122] This may result from venous stasis due to concomitant cirrhosis, neoplastic obtrusion or both. With these possibilities in mind, the sudden exacerbation of symptoms related to portal hypertension[38] or the appearance of evidence of inferior caval obstruction[122] should occasion prompt suspicion of hepatoma in the case of the patient with cirrhosis.

Ductal Neoplasm (Cholangioma). The cholangioma has no predilective site or characteristic gross configuration. It frequently

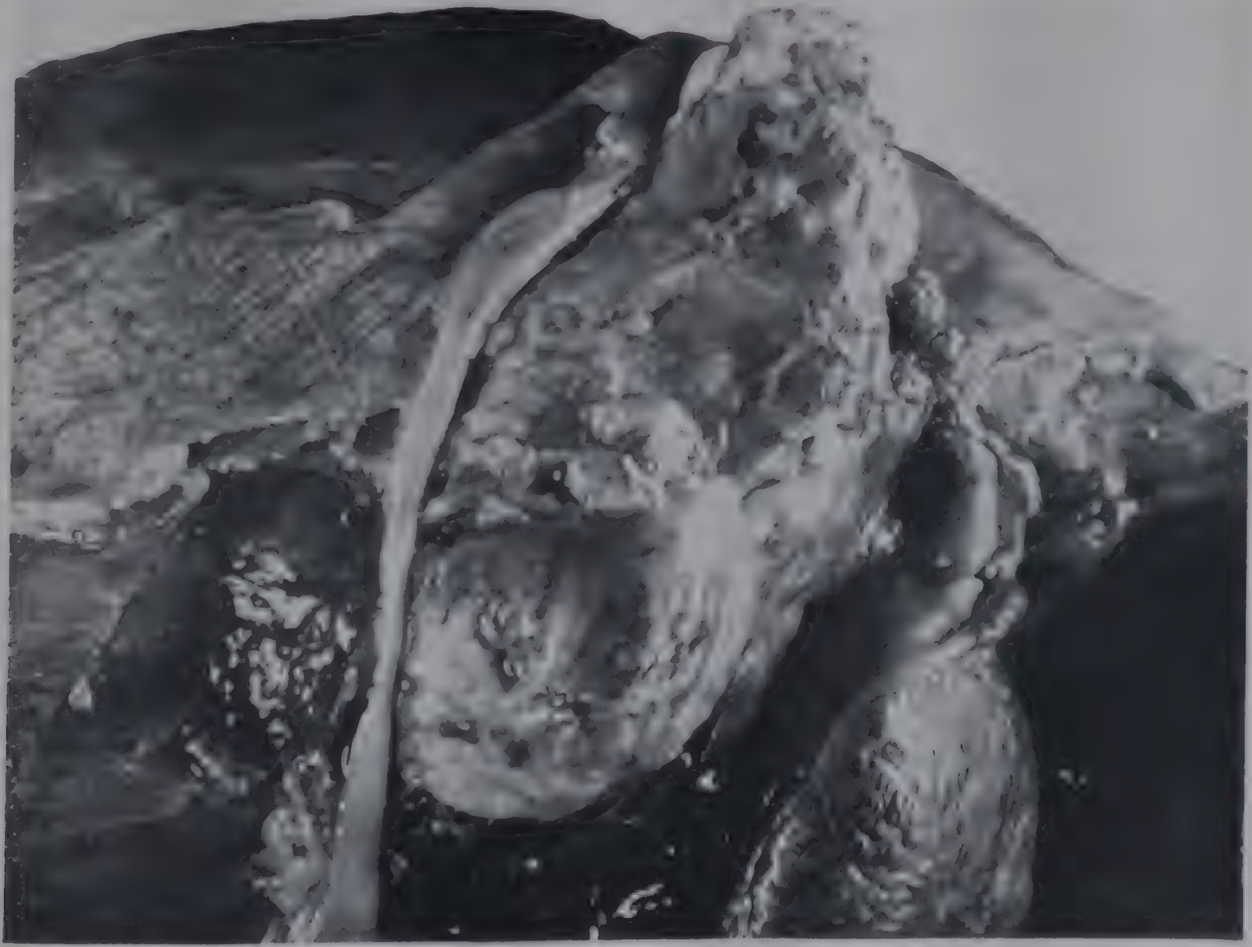


FIG. 162. Hepatoma. A tumor thrombus projecting into the inferior vena cava as a polypoid mass emerging from the hepatic vein.

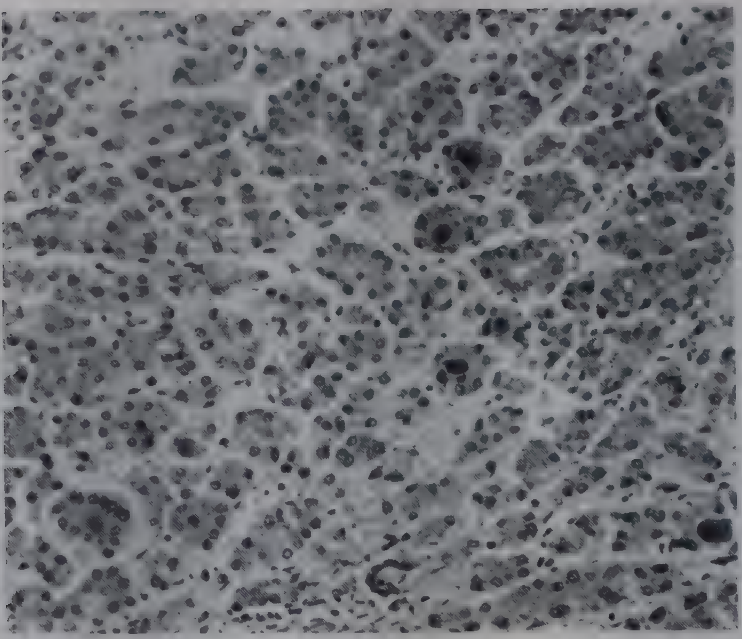


FIG. 163. Hepatoma. A photomicrograph demonstrating a papillary and trabecular pattern. The narrow fronds extend among sinusoid like channels and there is relatively little stromal component. In the center of pseudoacini may be seen small droplets of inspissated bile. (× 160)

appears as a single large, rather homogeneous, grayish-yellow mass which simulates metastatic carcinoma. Umbilication is seldom present, and a heavy stromal component gives it a more scirrhous quality than hepatoma. Seedling metastases often occur throughout the liver, but the primary tumor is dominant. The surrounding liver is smooth, noncirrhotic but may be deeply stained with bile, a feature contrasting with the tumor itself, which is not pigmented. Bile stasis of this order occurs only when the tumor, by reason of its location, obstructs major ducts. Venous obstruction is not common, and portal thrombosis, when it does appear, is usually a result of secondary cholangitis and not tumor thrombosis. This form of tumor is not highly vascularized, and hemorrhage from it is not a common event.

Combined Form (Hepatocholangioma). This lesion resembles hepatoma in its gross characteristics and has no peculiar features which permit ready distinction.[2] It is probable that it is closely related to tumors of parenchymal origin and may well be a variant of that group.[38]

MICROSCOPIC PATHOLOGY

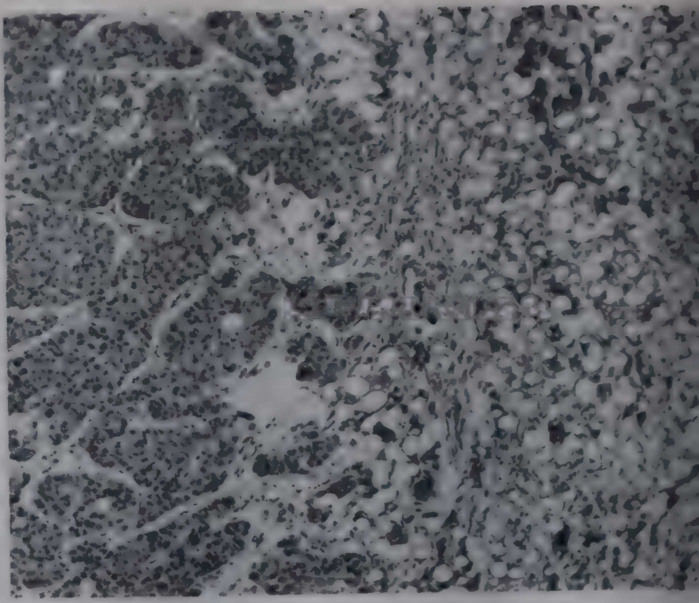


FIG. 164. Hepatoma. An alveolar pattern in which contrast between the neoplastic cells devoid of lipid and the markedly vacuolated surrounding parenchyma is well shown. (× 80)

Hepatoma. The hepatoma exhibits a considerable range of cytologic structure a
functional capacity. In the differentia
neoplasm function is manifested by the
cretion of bile.[60] Droplets appear wit
tumor cells, between them or within ac
(Fig. 163). Though not manifested u
formly in all hepatomas, bile formation is
diagnostic aid when demonstrable.[74] Disti
tion of this pigment from hemosiderin, wh
may be abundant in hemorrhagic foci, u
ally is made with ease, although it may
necessary to have recourse to iron stains
is of interest that hepatomas occurring
cases of hemochromatosis rarely contain s
nificant amounts of the iron pigment so ab
dant elsewhere in the liver.[122] An except
to this is the case reported by Binford a
co-workers.[17, 110]

Glycogen is also disproportionately sca
in hepatoma cells, although present in la
amounts in the parenchyma.[75] Here, too,
ceptions occur, and the clarity of cytoplas
staining under such circumstances may
mit simulation of new growths of renal
adrenal origin. This may well be an expla
tion for the disputed primary intrahep
hypernephroma. Vacuolization due to in
cellular lipid is also improminent in
hepatoma cell, and its sparsity may cont
the neoplasm very sharply with the surrou
ing fat-filled parenchyma (Fig. 164).

The regularity of pattern is rarely of s
order as to create much difficulty in

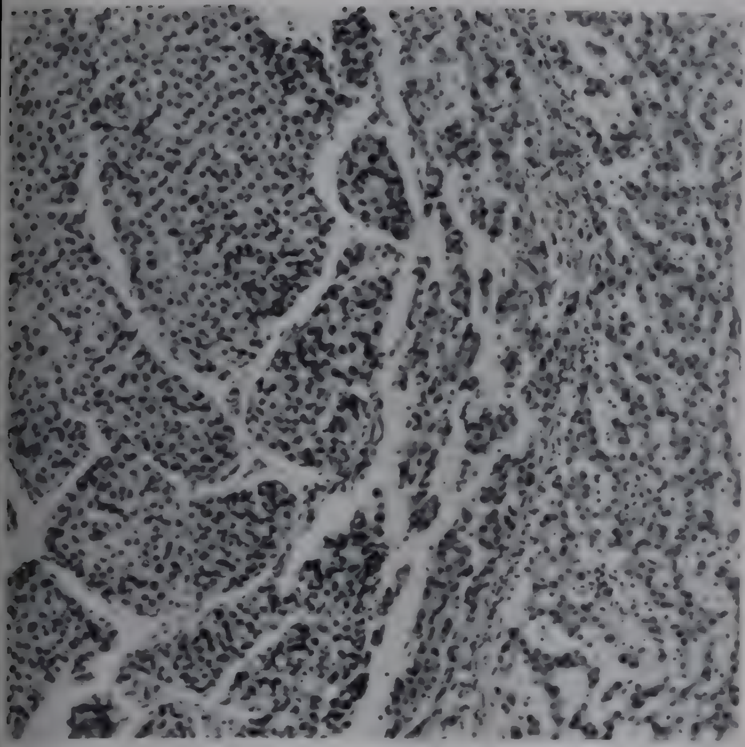


FIG. 165. Hepatoma. Solid masses of neoplastic elements exhibit no resemblance to adjacent parenchymal cells. (× 80)

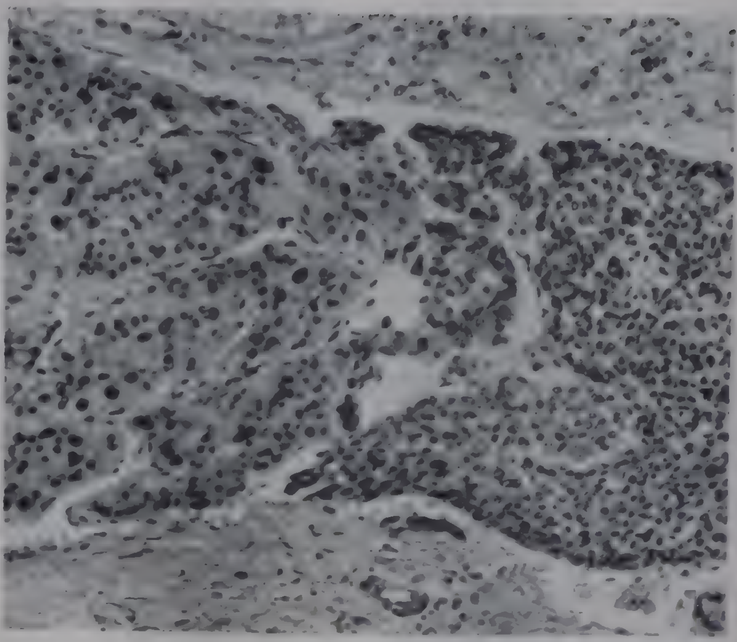
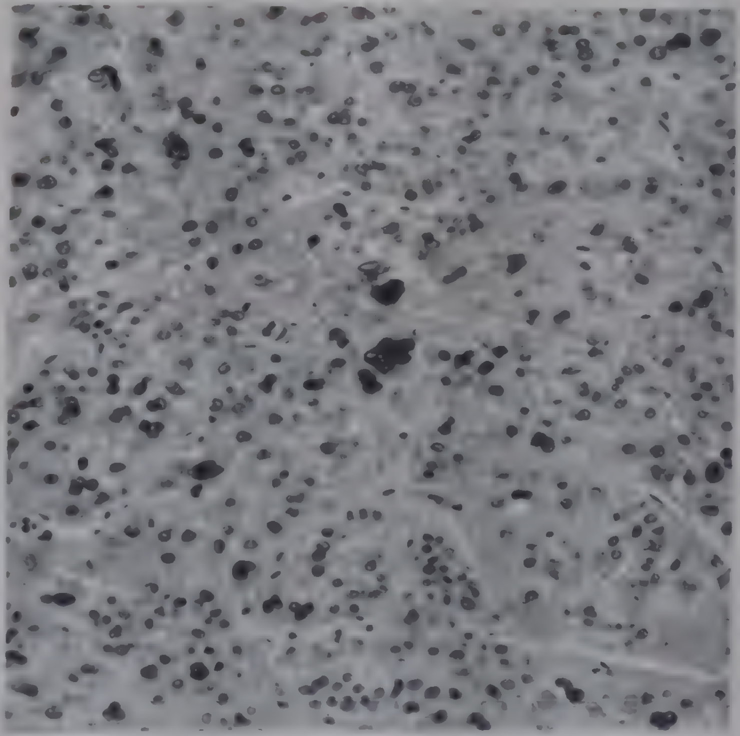


FIG. 166. Hepatoma. (*Top*) An undifferentiated form with large syncitial masses and bizarre nuclei to the left and a patternless small-cell component to the right. A resemblance to chorio-epithelioma is apparent. (× 160) (*Bottom*) Closely packed syncitial hepatoma elements with bizarre multinucleated forms. (× 160)



tinguishing the nodule of hepatoma from the actively regenerating nodule of cirrhosis.[122] Even when this does occur, contrast of the component elements in adjacent liver substance usually suffices (Fig. 165). Nuclear irregularities, cytoplasmic peculiarity coupled with the absence of bile duct residua and Kupffer cells are helpful distinguishing features.

The most common growth pattern encountered is of a papillary or trabecular variety (Fig. 163). In this form there are cords of large polyhedral oxyphilic cells coursing as narrow fronds one or more cells thick. These are embraced by a delicate layer of flattened endothelium which in turn faces upon a sinusoidal network containing greater or lesser amounts of blood.[60] Stroma is scanty in relation to these channels but may be present as occasional coarse trabeculation, causing lobulation of the tumor. Less frequently encountered is an alveolar structure characterized by thick, rather solid masses of epithelium in some of which frank acini appear[74] (Fig. 165). In the instances in which acinus formation predominates the structure of cholangioma is simulated and may lead to a mistaken classification as hepatocholangioma. Acinar cells are usually polyhedral, but they may be tall and columnar; on occasion they have been observed to be ciliated. Secretion is either bile or a brightly eosinophilic hyalin substance of unknown nature. It does not have the filmy basophilia of the mucoid material secreted by ductal epithelium. A third variant exhibits little organoid pattern and consists of irregularly arranged large anaplastic cells containing one or more hyperchromatic or vesicular nuclei[74] (Fig. 166). The latter have bizarre

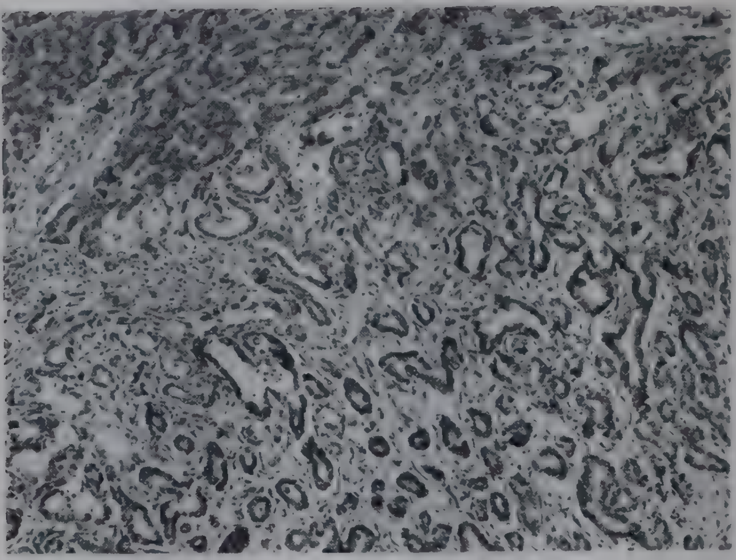


FIG. 167. Cholangioma. A well-differentiated adenocarcinoma characterized by ductlike acini embedded in a fibrous stroma. Epithelium is relatively uniform in appearance and arrangement. (× 80)

configuration and may be observed in process of division. The large pleomorphic cells with multiple nuclei bear some resemblance to abnormal placental trophoblast and probably represent the elements which have comprised so-called primary chorio-epithelioma of the liver.

Cholangioma. Much more scirrhous than the hepatoma, the epithelium here is embedded in a relatively densely collagenized stroma which is not strikingly vascularize Acinus formation is the rule, and ordinari these structures are well differentiated. They are lined by short, simple columna epithelium with a fair degree of uniformit (Fig. 167). There is nuclear dyspolarity, an the glands have no regularity of size or di tribution. Mucus secretory activity may b noted, but there is no bile production. U differentiated cholangiomas are uncommo

The histologic resemblance to tumors extrahepatic bile duct, gallbladder, or pa creatic origin, and indeed to those arisi in other portions of the alimentary tra may be striking.[60] A distinction betwee cholangioma and a metastatic lesion ste ming from one of these sites cannot be mad on histologic grounds alone. It is necessa to exclude the possibility of an extrahepat point of origin.

Hepatocholangioma. Clear-cut exampl of this combined form of tumor are co paratively rare, and it is likely that ma recorded instances represent acinar varian of hepatoma or undifferentiated forms cholangioma[2] (Fig. 168). It is not surprisi that difficulty in determining parenchym or duct-cell origin exists. In examining se tions of liver in areas of active repair fo lowing various forms of injury it is commo

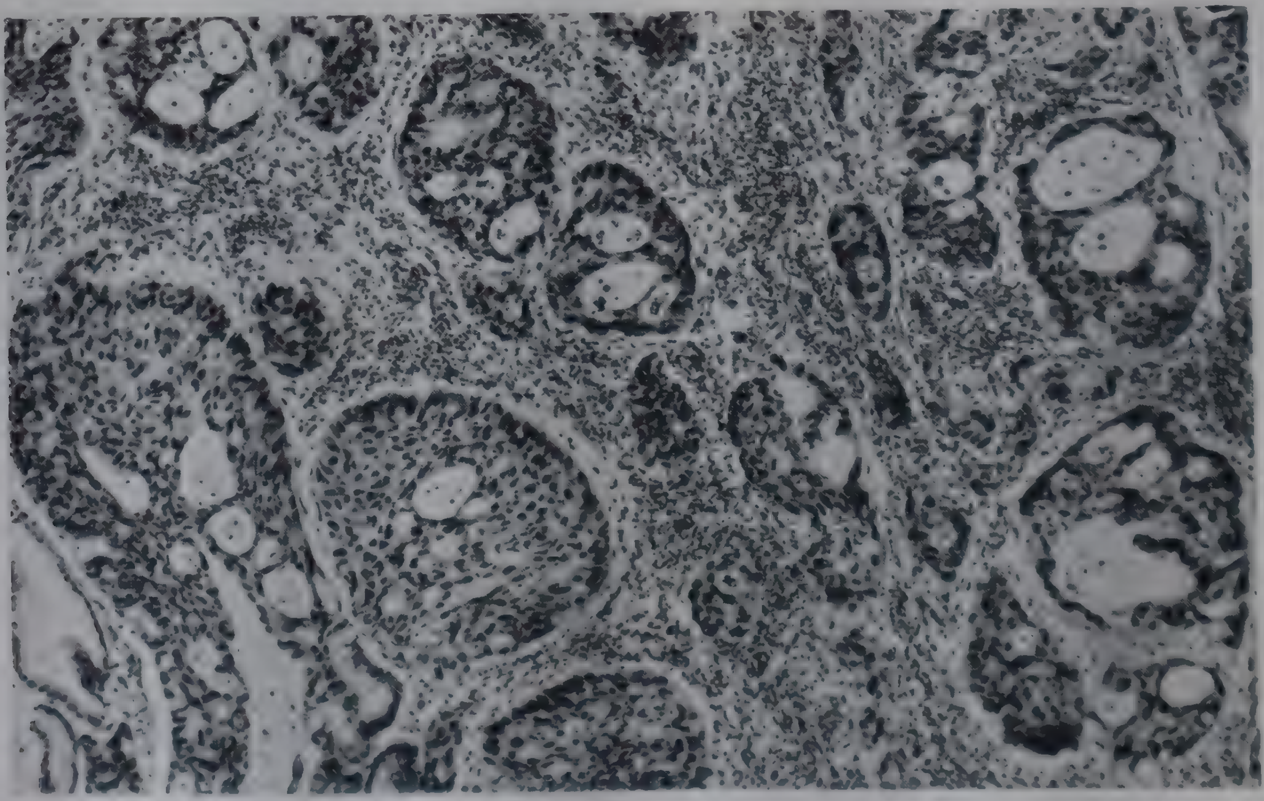


FIG. 168. Hepatocholangioma. Masses of hepatomalike parenchymal cells in which illy formed acini appear. (× 80)

place experience to encounter foci in which cords of cells are seemingly parenchymal at one terminus and ductal at the other.[76] There is controversy regarding the interpretation of this phenomenon, but there is no disagreement as to its existence. It may be presumed, however, that this feature observed in non-neoplastic conditions may occur also in tumors.

Extrahepatic Metastasis. Despite general opinion, metastasis from tumors of the liver is not rare, although it occurs with less frequency than with lesions primary in other viscera.[50, 122] In our own series[43] two thirds (hepatoma, 65%; cholangioma, 67%) of the cases exhibited extrahepatic metastasis at necropsy. From the literature one gathers that the experience of others indicates dissemination of tumor in 20 per cent to 66 per cent of cases.[35, 40, 52, 53, 71, 114, 122] It is claimed by some that metastasis is more common with cholangioma.[38]

Favored sites are the lymph nodes in the hilar and the peripancreatic regions (particularly with cholangioma), the lung, the pleura, the peribronchial nodes and the peritoneum.[50] The brain, the adrenal and the osseous systems are involved occasionally.[25] In a group of 55 cases of hepatoma[43] there were 7 with metastasis to the lung only and 7 others with multivisceral involvement. Bone metastasis occurred in 2 patients, and brain metastasis in one. It is said that involvement of the osseous system occurs in 1.6 per cent of patients with hepatoma.[18] Among 22 cholangiomas[43] lung and bone each contained metastasis in 3 cases, and in 6 there was widespread distribution.

CLINICAL MANIFESTATIONS

Gustafson found that a correct antemortem diagnosis of primary liver carcinoma was made in only 11 per cent of cases.[53] In another series clinical recognition was accomplished in 30 per cent, but in several of these the diagnosis was aided by laparotomy or biopsy.[122] Others have recorded equal clinical inaccuracy, a situation which obviously is attributable to a low rate of incidence and an absence of specific manifestations.

Suspicion of neoplasm should be aroused in the event of an inexplicable acceleration of symptoms in an individual with quiescent cirrhosis.[38] Also, the possibility should be entertained in a patient with cirrhosis who has concomitant evidence of a malignant tumor, or one who has neoplasm of the liver in whom a primary site is inapparent.[38]

In good part the manifestations associated with liver cancer are those which may be attributed easily to cirrhosis. Among these are ascites, anemia, weakness and splenomegaly. Of greater pertinence, particularly when associated with the aforementioned, are upper abdominal pain, liver tenderness, jaundice, bloody ascites, sudden intraperitoneal hemorrhage, abdominal mass, irregular nodularity of the liver, peripheral edema, unexplained fever and exacerbation of ascites. Leukocytosis, increased glucose tolerance, insulin shock[40] and cachexia are less definitive and less common signs. Berk and Lieber propose that serious consideration be given to the possibility of hepatoma in an individual with hemochromatosis in whom there appear pain, jaundice and an amelioration of the existing diabetes.[14] Also, it has been pointed out by Schatzki and others that roentgenograms revealing elevation, fixation and irregularity of the diaphragm in patients with esophageal varices and/or cirrhosis may be helpful in detecting hepatoma.[40, 103, 119]

PROGNOSIS

This is uniformly poor; few cures are recorded.[40, 53, 73, 114, 120] Almost all patients succumb within 1 year of the onset of symptoms, although an isolated survival of 46 months has been reported.[71] It is claimed that duration is slightly longer with cholangioma, but this is a moot point. Death is the result of metastasis, portal-vein thrombosis, hepatic failure, intraperitoneal hemorrhage or infection superimposed upon cachexia.

TREATMENT

Efforts to resect solitary neoplasms of the liver, although fraught with the serious hazard of intractable hemorrhage, have met with some technical success.[12, 63, 96] However, in the case of primary hepatic carcinoma there has been little alteration of prognosis.[31, 122] Instances of alleged success appear for the most part in the older literature, and in many the adequacy of microscopic interpretation and of follow-up leaves much to be desired. Benign tumors, particularly if limited to the left lobe or attached by a pedicle, lend themselves more readily to extirpation.[89] It is likely that many of the successful surgical procedures claimed were carried out on lesions of this nature.

Roentgen therapy has offered little of benefit. It has been suggested that nitrogen mustard and related compounds administered intravenously or introduced directly into the hepatic artery may have some value.[89]

BENIGN EPITHELIAL NEOPLASM

Benign tumors of hepatic parenchyma and ducts are rare and require little added discussion. Most of the data pertaining to their malignant counterparts apply to them as well.

The term "benign hepatoma" is often misused to indicate a liver nodule which is not truly neoplastic (i.e., hamartoma, localized area of regeneration, etc.). In the instance in which the process is indeed neoplastic its structure resembles that of the well-differentiated malignant hepatoma. It is questionable that a distinction can be made between the two on cytologic grounds alone.[120] Much the same situation exists here that is encountered in the small parenchymal adenomas of the kidney and other secretory organs. It has become customary with many of these to utilize gross size as an indicator of prognostic implication. With respect to the kidney it is generally conceded that cortical adenomas of small size (less than 2.5 cm.) are to be considered as benign; those larger are to be regarded as malignant.[59] A similar policy seems to be justified in the case of the hepatoma, presuming that the histologic structure obviously is not that of a malignant tumor.

Minute bile duct adenomas are not observed too rarely in routine necropsy studies of the liver. They are usually of microscopic proportions, and their appearance is such as to raise a question of a neoplastic versus a regenerative background. Despite circumscription they resemble the localized ductular proliferation observed in response to injury. In the rabbit and other animals adenomatous hyperplasia of bile ducts is common concomitant of helminthiasis. also occurs in the human subject in area in which hepatic parasitism is frequent.[1 As in the case of the hepatoma, it woul seem that the size of an intrahepatic cholar gioma has greater prognostic significanc than its histologic structure. The latter characteristically relatively bland and orderl

ENDOTHELIAL NEOPLASM

Angioma constitutes the most commo tumor encountered in the liver. A freque lesion in many locations in the body, th liver represents its most common viscer site.[107] Its incidence here is second only that in the skin and mucous membrane.[46]

Lesions of endothelium of this nature a believed by many to be non-neoplastic di orders of growth, i.e., hamartomas.[62, 113, 1 This may be the case in the benign for but there can be little question as to t neoplastic qualities of the malignant an oma. According to some[42] they derive fro embryonic endothelium or may represent di placed rests of the vascular anlagen.[97] Th are more common in the female (2 4.5:1)[15] and may be encountered at all ag from the newborn period to old age.[42, 48, In rare instances blood vessel tumors of t liver may be indicative of a familial tr and can be associated with systemic angi matosis.[68, 78, 117, 124]

Angiomas occur more frequently in t left lobe of the liver.[15] They usually app as small discrete reddish-purple nodules w a spongy texture and may be located at a level in hepatic substance. With involuti the florid hue is lost, and the lesions beco grayish white or rusty yellow and have fibrous consistency.[124] Spotty calcificati may be manifest, but this is less comm in the liver than in angiomas elsewhere the body.[6] They seldom protrude above t surface but may do so and may even pedunculated. Rarely exceeding 2.5 cm. diameter, they have attained the size of child's head[96] and a weight of 2,500 Gm A diffuse hepatic nodularity can result fr a myriad of minute and coalescent angiom or there may be a curious noncircumscri interdigitation of bare endothelial chan among the parenchymal elements. This is most unusual in the human subject and resembles a peculiar hepatic telangiectasis appearing in cattle.[99] A liver that is the seat of a disorder of this nature is large and bulky and appears as a deeply purple-tinged turgid mass.

The microscopic structure of the great majority of angiomas is of the banal cavernous nature. The endothelium-lined sinuses are supported and separated by broad fibrous strands in which extravasation and hemosiderin deposits are common. Encapsulation is not the rule despite the prominent fibrous framework, and the tumor sinuses blend imperceptibly among the hepatic sinusoids. In the case of the capillary angioma the insinuation of its endothelial buds may be distinguished from the normal sinusoids with difficulty. A recognition of the absence of Kupffer cells in the tumor sinuses will aid in this distinction. Except in the instance of lymphangioma[118] these sinuses contain red cells in abundance and are the seat of thrombosis and organization.

The malignant form of endothelial neoplasm is variously termed endothelial sarcoma, endothelioblastoma, angioblastoma, angiosarcoma, malignant angioma, etc. This is a nodular though poorly delimited process widely infiltrative and strikingly hemorrhagic. Abortive efforts at vessel formation result in poor lumen development and the appearance of solid cords of pleomorphic endothelium, exhibiting nuclear variations and mitotic figures in relative abundance (Fig. 169). Resemblance to the more vascular and anaplastic forms of hepatoma is apparent. One should avoid such errors of interpretation.[38, 72] Metastasis can proceed widely by way of the blood stream, but this is not common. Death is more often the result of hemorrhage.

Since most angiomas are small and innocuous, there are no related clinical sympoms.[6] They almost invariably represent ncidental observations at exploration or necropsy. However, when significant bulk is attained the symptoms are essentially those of hepatomegaly from any cause, although intra-abdominal hemorrhage is a common complication. Indeed, as in the case of hepaoma, this may be both the initial and the fatal presenting manifestation.[38] A murmur or a venous hum may be audible through the abdominal wall in more extensive lesions, and a thrill may be palpable.[73] These are unusual phenomena, however, and are not at all pathognomic, since they have been encountered with vascular hepatomas and in relation to other masses in this portion of the abdomen. Calcification in hemorrhagic extravasates may be visible in roentgenograms, but the degree of mineralization is generally very slight. Similarly located opaque deposits occur with tuberculosis, echinococcus disease, hepatolithiasis and subphrenic or liver abscess. The unique lesion reported as an "endothelial sarcoma" by MacMahon, Murphy and Bates[77] was highlighted roentgenographically by previously administered (12 years) Thorotrast, which in this instance was also presumed to be the cancerogenic agent. Despite the terminology, this tumor was not a vascular lesion but one comprised of phagocytic histiocytic elements classified by the authors as endothelial leukocytes.

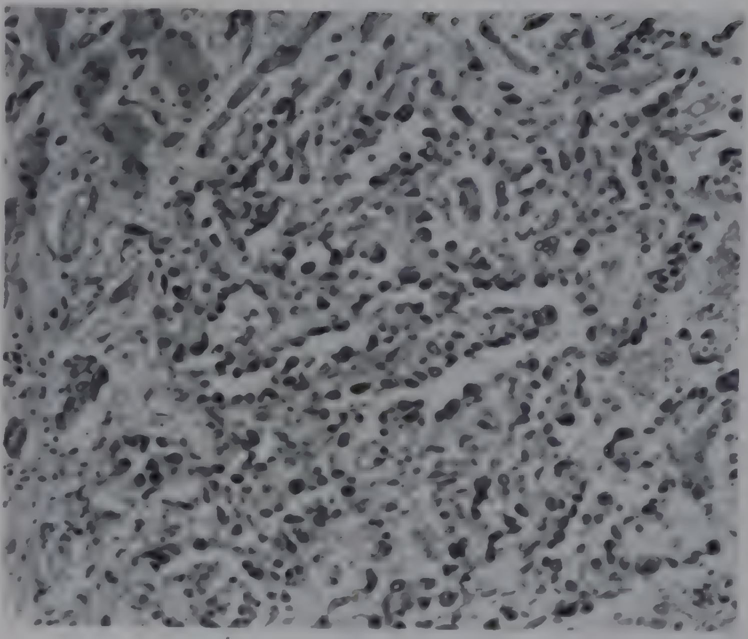


FIG. 169. Malignant angioma. This liver was diffusely infiltrated by narrow channels resembling capillaries lined by bizarre endothelial cells. (Armed Forces Institute of Pathology, A.F.I.P. Accession 607019. × 160)

Angiomas rarely require therapy. In the rare instance of a pedunculated lesion of sufficient size to require removal, resection is relatively simple, provided that due regard is given to the prevention of hemorrhage

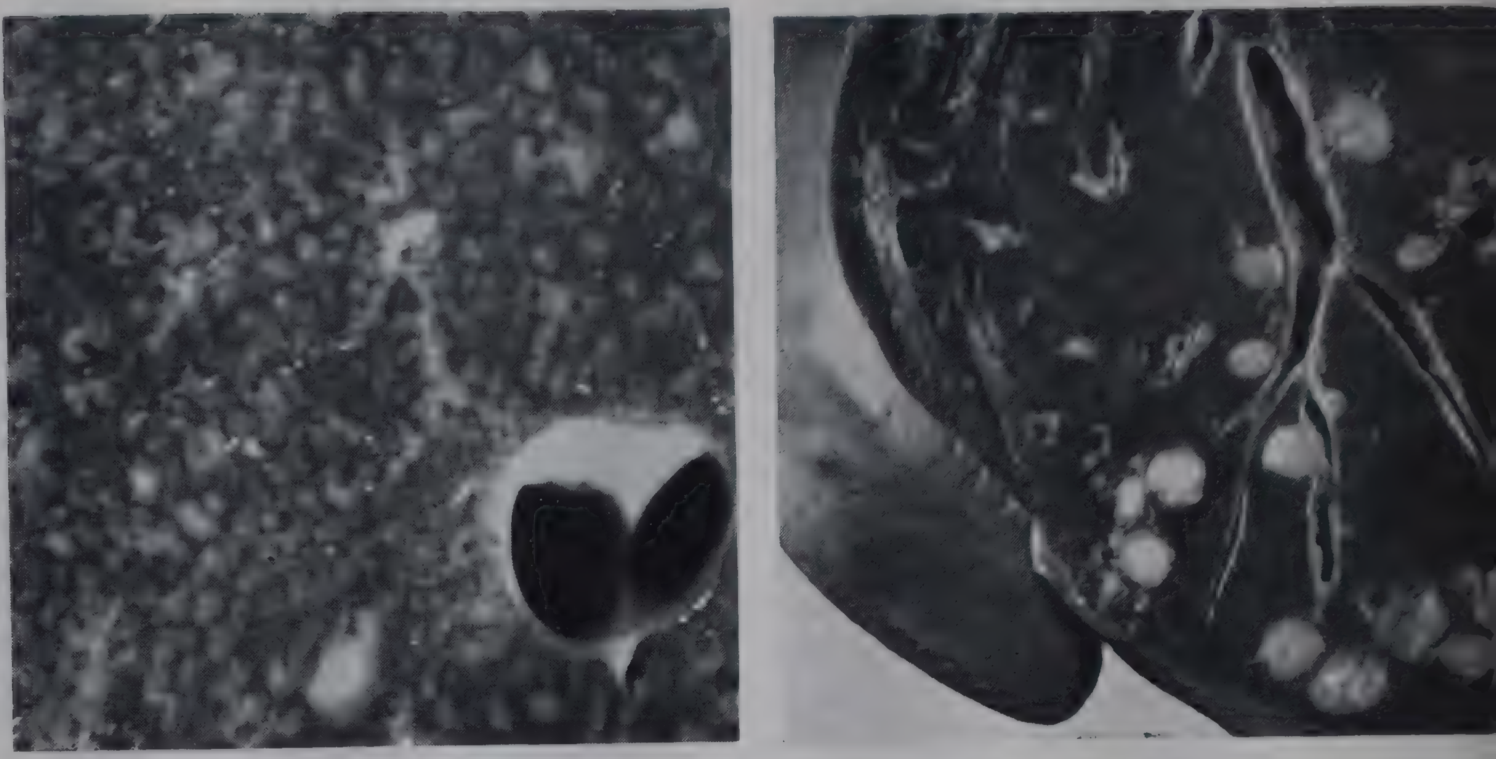


FIG. 170. (*Left*) Myeloid leukemia. A close-up view of a sectioned liver, demonstrating a prominent though irregular streaking indicative of leukemic infiltration. (*Right*) Hodgkin's disease. A transverse section of the liver exhibiting nodular aggregates in malignant lymphoma.

from the liver bed.[63, 107] The large tumors that are inaccessible to surgery are benefited by roentgen therapy in some instances. Ray[96] has reported a large deep-seated cavernous process in which x-ray treatment was remarkably effective.

Prognosis is affected by the extent and more particularly by the histologic nature of the angioma. It is rare, even with the large benign lesions, that serious implications exist, although there is danger that trauma to the liver in the presence of a bulky angioma may result in intractable hemorrhage.[6] On the other hand, the malignant angioma pursues a rapidly fatal course once its presence becomes manifest.[42, 117]

HEMATOPOIETIC NEOPLASM

This group does not properly represent primary hepatic neoplasm. It is essentially indicative of liver involvement as part of systemic disease. Only in the exceptional case is the liver the sole or predominant site of the disease. Infiltration is common in myeloid leukemia but it is seldom seen in the monocytic form. On the other hand, the liver is often the seat of diffuse or nodular lesions in malignant lymphoma with or without lymphatic leukemia, the degree and th nature varying with the type of lymphoma.

The enlarged organ is generally smoot and pallid and exhibits little else to gros inspection. Fine streaklike infiltrations ar observed occasionally (Fig. 170, *Left*) an in rare instances discrete nodules simulatin metastatic carcinoma have been noted (Fi 170, *Right*). The latter circumstance is en countered more often in Hodgkin's diseas and reticulum-cell sarcoma; it is exceptiona in other blood dyscrasias.

The microscopic picture is identical wi that observed in leukemia and lymphom elsewhere in the body. There is a monot nous repetition (save in Hodgkin's disease of whatever cell or pattern of growth cha acterizes the disease in a given patien Frequently, portal areas are enlarged u formly by the cellular infiltrate and this in parts the streaking observed with the unaide eye. Unusual focal growth leads to coar nodularity. In certain forms, notably in my loid leukemia, the sinusoids are made undu prominent by heavy aggregations of leukem myelocytes.

Smooth enlargement of the liver, fr quently accompanied by splenomegaly, w a dragging sensation in the upper abdom are the nonspecific features directing clinical attention to this condition. As a rule the clinical syndrome is dominated by the usual systemic manifestations of leukemia. Jaundice is rare in the absence of complicating sepsis, and abnormality of liver function is variable and nonspecific. Despite the absence of symptoms pertinent to hepatic involvement, patients with the malaise attendant upon leukemia have a surprising degree of relief and even euphoria following roentgen therapy to the enlarged liver.

Needle biopsy of the liver has proved to be a valuable diagnostic adjunct in the hematopoietic disorders. A correct diagnosis has been established on several occasions in cases in which the peripheral blood picture has been equivocal and conventional marrow puncture has been unsuccessful.[104]

SUPPORTING TISSUE NEOPLASM

This group consists of fibromas, lipomas, leiomyomas and myxomas and their malignant counterparts. They are probably rare. although their incidence cannot be determined with certainty, since they constitute only minor incidental lesions at necropsy and seldom attain proportions which permit clinical recognition. Consequently, unless attended by extraordinary features they do not reach the medical literature. The few which do would seem to indicate a predominance of malignant forms, a situation which is undoubtedly more apparent than real. Shallow and Wagner[108] believed that fewer than 100 cases of sarcoma of the liver had been recorded. Herxheimer referred to 149 cases, but admittedly these were selected uncritically and probably included, among others, cases of lymphoma and metastatic lesions.[58]

Sarcomas of the liver have no special qualities that distinguish them clinically. The incidence in childhood appears to be disproportionately high, but the process is by no means limited to youth.[37, 73, 108] They are prone to be bulky tumors, comparatively

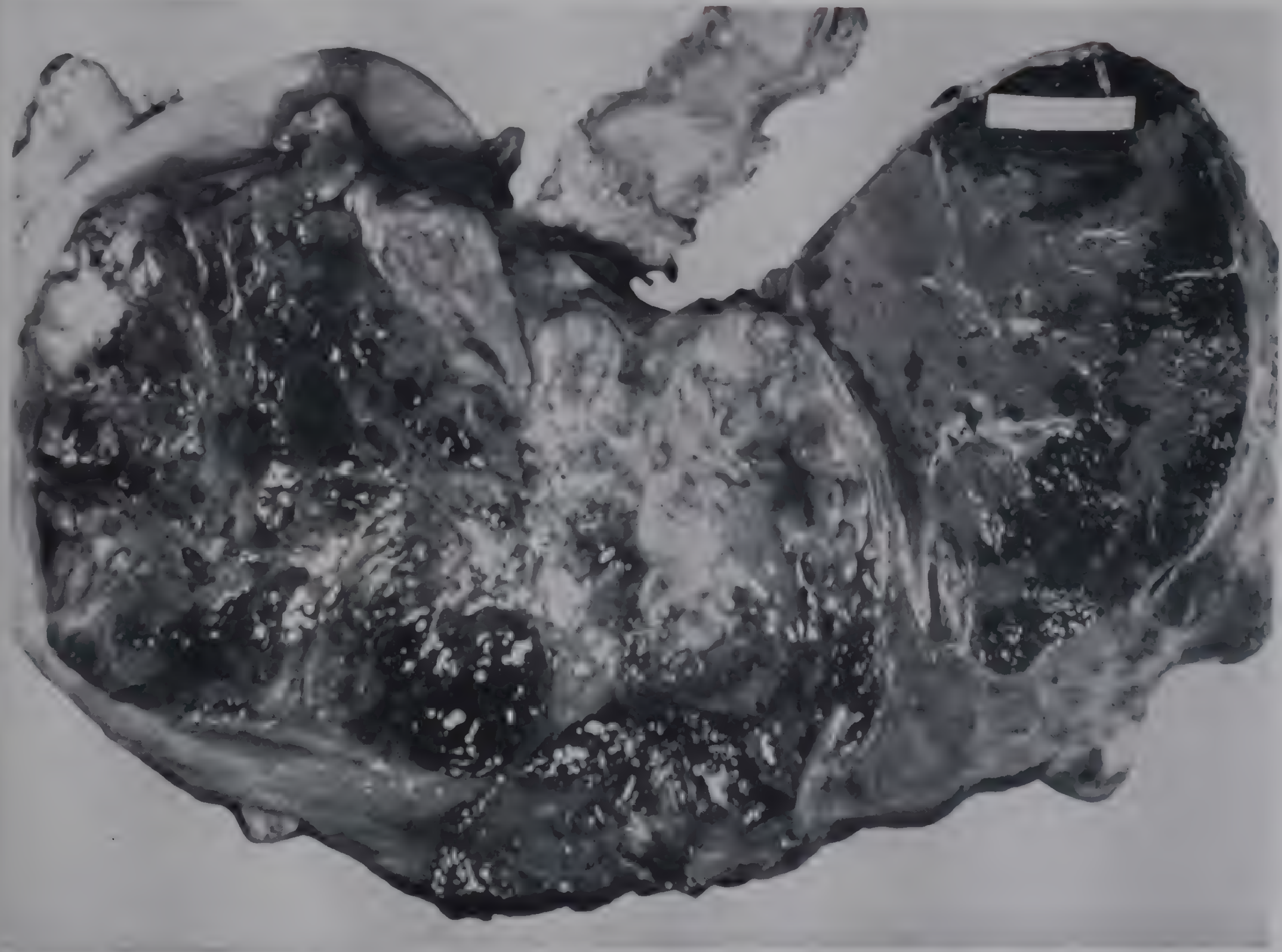


FIG. 171. Sarcoma of the liver. A huge sarcoma of the liver in the adult, replacing all of the right lobe. The tumor is cystic and necrotic.

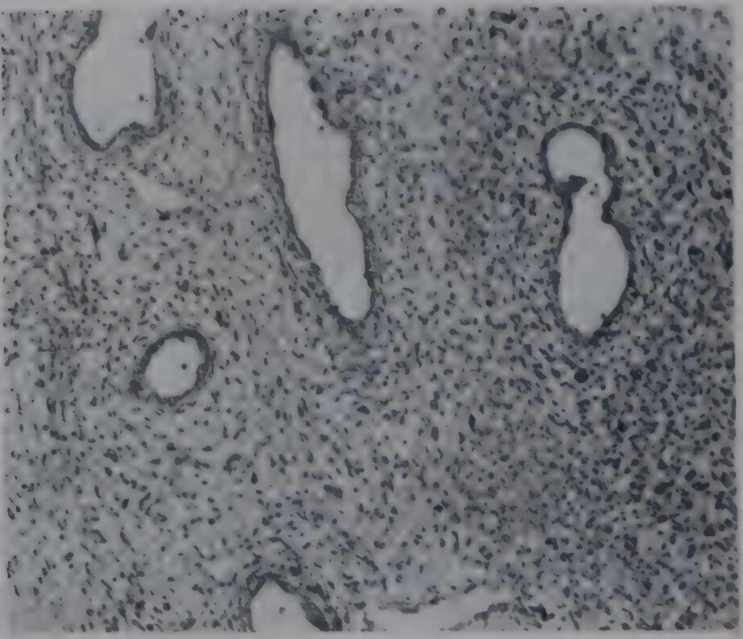


FIG. 172. Sarcoma of the liver. The lesion is obviously stromal, although dilated ductal elements may justify a diagnosis of carcinosarcoma (or adenosarcoma). However, the lining epithelium does not appear to be neoplastic. The photograph indicates the marked variation of cellularity observed in these lesions. (× 80)

soft, hemorrhagic and are often cystic (Fig. 171). A translucent viscid quality is noted on sectioning.

The histologic structure is often bizarre and is unlike that in sarcomas encountered elsewhere in the body.[11] Ewing stated that a pure spindle-cell sarcoma with uniform structure had yet to be described in the liver.[38] The nomenclature for these tumors is representative of their unusual structure; i.e., myxosarcoma, rhabdomyosarcoma and alveolar, spindle-cell, round-cell, giant-cell, angioplastic or angioreticular, perithelial, syncitial and anaplastic sarcomas.[81, 82, 109, 123] They are often so pleomorphic that it is impossible to classify them definitively. A lesion that appears to be a sparsely nucleated myxoma in one area may have spindle cell or striated myoblast aggregates elsewhere and also may contain islands of bone or cartilage (Fig. 172). Epithelial components are encountered, but these may represent the residua of normal ducts included within the neoplasm. Despite evidence of rapid growth, metastasis is unusual.[61] Death occurs as the result of hemorrhage, necrosis, cachexia, secondary infection or widespread infiltration of the abdomen with displacement vital viscera. A considerable number su cumb postoperatively following unsuccess efforts at removal.

TERATOID AND EMBRYONAL NEOPLASMS

These exceptional lesions constitute interesting group with curious morpholo variations. The adult teratoma and derm cyst are identical with like lesions encou tered more commonly elsewhere.[57, 85] I properly included in this category are th adenomas or cholangiomas in which me plastic cartilage or bone is found.[45, 106,] These are observed infrequently and somewhat more common in children. Der oid cysts also have been described in the f ciform ligament and the umbilical cord.[57,]

Millman and Grayzell found reports only 27 cases of poorly differentiated mi or embryonal tumors of the liver.[82] Term "carcinosarcoma," "mixed embryonal tum or "embryonal hepatoma," some of th resemble the embryoma (Wilm's tumor) the kidney. They are composed of loo edematous myxoid stroma, occasionally w islands of poorly developed cartilage osteoid and isolated strands of primit striated muscle. Anaplastic epithelium pears to emerge from stromal cells. It mains in an undifferentiated state or, as the Wilm's tumor, proceeds to the devel ment of bizarre ductal and acinar organ structures (Fig. 173). In a few examp well-differentiated foci of fetal parenchy appear.

It is probable that included among embryonal mixed tumors are instances of bizarre sarcomas described in the preced section. A clear separation is not always p sible, although it would seem to be w to reserve the designation of embry mixed tumor for those with both stro and epithelial neoplastic components.

Therapy would appear to be fruitles the malignant lesions; all of the reco cases have been fatal. There is no infor tion available as to radiosensitivity. In of the encouraging results with roen therapy in the Wilm's tumor and its s larity of structure to the embryonal tu

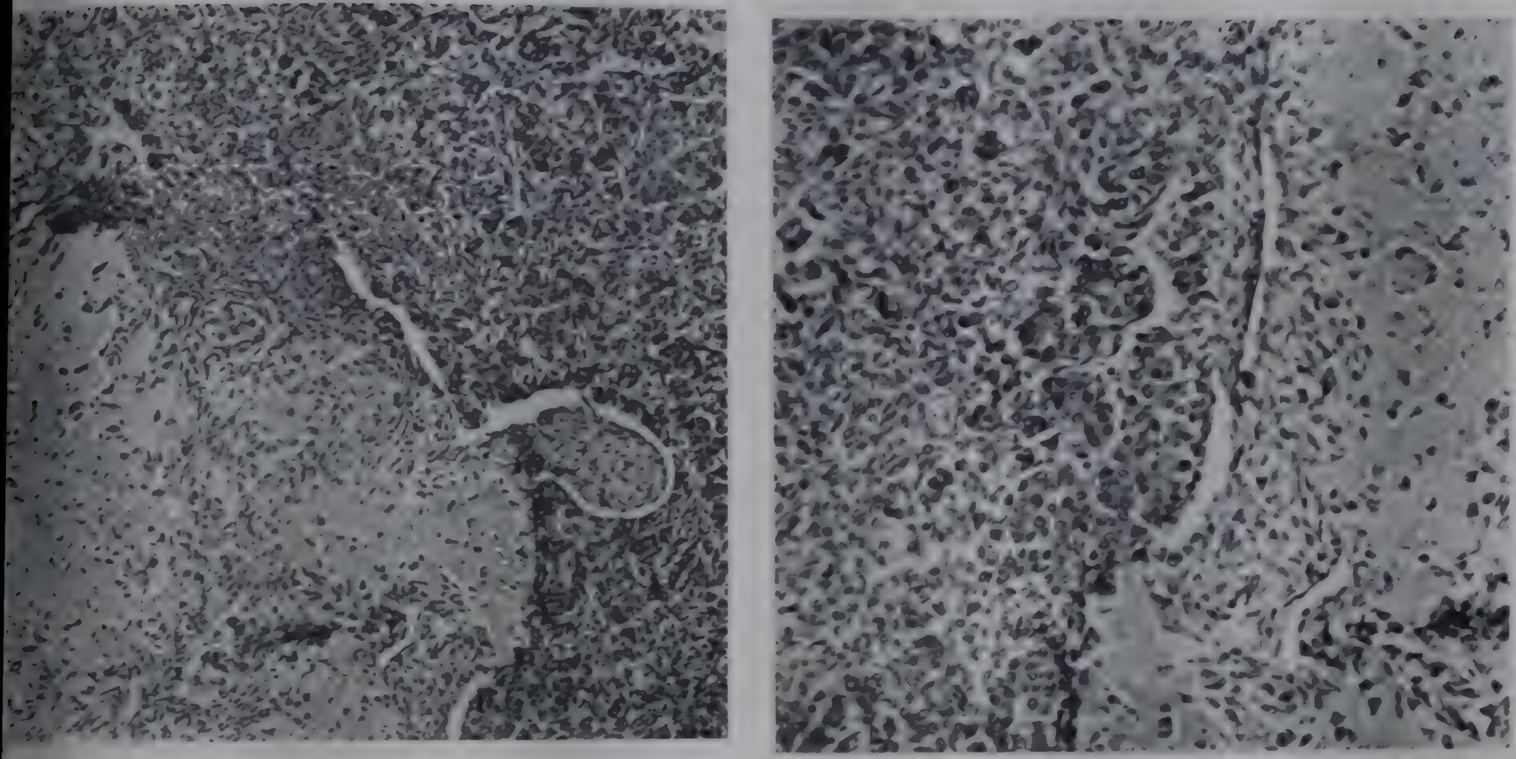


FIG. 173. (*Left*) Malignant embryonal tumor. A large island of osteoid is surrounded by a highly cellular neoplasm in which epitheliumlike clusters appear to emerge from an embryonal stromal background. (Armed Forces Institute of Pathology, Accession 497787. × 160) (*Right*) A high-power view of the lesion shown in Figure at left. The cellular stromal lesion exhibits abortive duct formation. The primitive character of the osteoid may be noted. (× 160)

f the liver, this would appear to be an venue of attack worthy of exploration.[69]

MISCELLANEOUS NEOPLASMS

In this group have been placed several ery rare neoplasms concerning which there as been controversy. It seems unlikely that uch lesions as "hypernephroma," "mela-oma" and "chorio-epithelioma" have valid laims to hepatic origin.

The normal anatomic contiguity of the ight adrenal to the posterior aspect of the ver is well known, and there is some indi-ation that aberrant adrenal substance em-edded within the substance of the right obe is more common than has been recog-ized.[9, 58, 105] The assumption that this may e a nidus for the origin of intrahepatic drenal cell neoplasm is reminiscent of the veary controversy relating to the cellular rigin of the so-called "hypernephroma" of he kidney. Most of the cases cited have een in the right lobe. There is no doubt hat neoplasm arising in an aberrant adrenal ocus is a possibility, but the cases cited in he literature are poorly documented and not convincing.[1, 95] In many, the possibility of metastasis from an unrecognized extrahepatic source or the direct invasion from a primary neoplasm of the adjacent kidney or adrenal has not been adequately excluded. It is also worthy of note that hepatomas may be composed of clear cells arranged in trabecular fashion and conceivably may be mistaken for adrenal cortical or renal tubular epithelium.

Few of the cases classified as primary melanoma of the liver withstand critical study. The liver is a well-known site of metastasis from melanoma of the skin and the ocular choroid. In each of these areas it is a common experience for an obscure minute primary tumor to remain unnoticed in the presence of massive visceral dissemination. It is also known that the excision of lesions of this nature may be followed by an unusually prolonged latent period before systemic distribution becomes manifest. Often physicians are confronted with metastatic melanoma in patients who deny or have forgotten the removal of a cutaneous lesion of innocuous appearance months or years earlier. Adherence to the dictum that a diagnosis of primary melanoma of the liver is permissible only after careful scrutiny of the eye and the skin probably would eliminate all of the cases cited.[58]

Primary hepatic chorio-epithelioma seems to be an even less likely entity than melanoma. A curious aberrance of genital epithelium or an origin in a teratoma appear to be necessary prerequisites. Undoubtedly, a significant number of the cases recorded represent anaplastic and syncitial-cell variants of hepatoma which have much cytologic resemblance to chorio-epithelioma. Undifferentiated bronchogenic carcinoma or obscure neoplasms of the ovary or the uterus are conceivable sources of hepatic metastases which also may simulate this condition.

METASTATIC NEOPLASM

Hepatic metastasis is anticipated in 35 to 50 per cent of all cases of neoplasm whatever the primary site.[15, 60, 73, 89] Indeed, secondary carcinoma is the most common malignant tumor encountered in the liver. It is estimated that the relative proportion of primary to secondary neoplasm in the liver is 1:20 with a range of 1:13 to 1:65.[15, 61, 124] The usual sites from which metastasis proceeds are the alimentary tract, the pancreas, the gallbladder, the lung, the breast, the genito-urinary system, the eye and the adrenal. Most of these enter the liver via the vascular system, the portal vein being a favored route. The hepatic artery serves as the avenue of entry in those cases in which pulmonary lesions of either primary or secondary nature exist. Retrograde lymphatic progression is a less common route.

Multiplicity is the rule in secondary neoplasm in the liver, the individual lesions being circumscribed and spherical in nature. Heavy infiltration and coalescence of adjacent nodules result in an irregular lobulated configuration. Enormous enlargement with weights up to 8,000 Gm. may result from massive seeding. Despite a high degree of parenchymal replacement, detectable jaundice usually is absent or relatively slight.[119] The distribution of metastasis in its early stage may follow the direction of flow of portal vein currents with predominant right-lobe or left-lobe involvement, depending
upon the venous drainage of the viscus c
taining the primary neoplasm.[8] This predil
tion is soon lost, however, as the degree
liver infiltration increases.

An enlarged, coarsely nodular liver or
which is relatively smooth but contains
eral discrete nodules palpable through
abdominal wall should arouse suspicion
metastatic tumor. Although metastasis
dom is observed in the cirrhotic liver,
is an inconstant restriction and does
indicate a specific immunity to metast
implantation. Whether this may be attr
uted to the limited portal blood flow
cirrhosis, to the age range of patients or
a lessened incidence of extrahepatic n
plasm has not been determined. It see
reasonable, nonetheless, to consider tha
cirrhotic liver exhibiting unusual nodulat
or other manifestations of neoplasm sho
be suspected of harboring primary rat
than secondary tumor.

The needle biopsy method has prove
be an unusually effective means of detect
metastatic tumors in the liver. Despite
seemingly blind approach, Safdi and
workers[101] and Bowden and Kravitz[19] s
ceeded in demonstrating neoplasm in
liver in 70 to 80 per cent of cases in wh
it ultimately was proved to be present. T
is a particularly noteworthy yield, since
degree of involvement in many was relati
sparse.

Recently, Yuhl and co-workers have p
posed the use of radioactive albumin a
tracer substance with disproportiona
higher predilective localization in hep
than in extrahepatic metastasis.[128]
method obviously requires further usage
refinement.

Overt derangement of liver function is
ordinarily apparent, although one or m
of the commonly utilized liver-function t
will exhibit abnormality in the presence
hepatic metastasis. Many investigators h
called attention to a disproportionate ris
the serum alkaline phosphatase under th
circumstances and have emphasized the
fulness of this test in anticipating other
obscure liver metastases.[21, 54, 78, 80] Bul
indicated that if cirrhosis, obstructive ja
dice and bone disease were eliminated,
serum alkaline phosphatase, although by

ans infallible, was a helpful indication of
plastic disease of the liver.[20] It is thought
be particularly helpful in the recognition
metastasis developing after abdominal op-
tions for extrahepatic carcinoma (colon)
en the liver was found to be free at the
e of laparotomy. Mendelsohn and Bodan-
observed considerable retention of brom-
phalein and other dyes but noted that
ılar abnormalities occurred quite fre-
ntly in the absence of metastasis.[79] These
hors found that 78 per cent of cases with
er metastases exhibited elevation of the
um alkaline phosphatase, a rise which
urred in only 10 per cent of cases in
ich metastasis was not present. Klotz
ted that 64 per cent of nonicteric patients
h hepatic neoplasm exhibited an abnor-
l rise of the serum alkaline phosphatase.[67]
iel and Shahon, on the other hand, were
convinced that any liver function test was
value as a search method for neoplasm.[5]
There appears to be no test that will de-
t minimal metastasis.[90] This is obviously
essential need when radical surgical pro-
dures are being contemplated.

PSEUDONEOPLASM

This is an unsatisfactory term, and there
no general agreement as to its meaning.
has been customary to consider as a
eudotumor or a pseudoneoplasm any clini-
ly detectable mass simulating a tumor that
oves to be non-neoplastic. Such lesions
ay be malformations of which the Riedel
aver-tail lobe is a prime example or an
uberant reaction to injury of infectious or
ninfectious nature.

Anomalous enlargement of one or an-
her of the minor hepatic lobes is not as
quent as the Riedel lobe but may create
me concern at abdominal exploration.[28]
peculiar knoblike projection is observed
otruding from the superior surface of the
er in infants in which central defects of
e diaphragm exist.[93] Aberrant hepatic sub-
nce may appear in the falciform ligament
contiguity with or separated from the
in liver mass.[106] In each of these the histo-
gic structure is essentially that of normal
er.

Infectious lesions, such as tuberculoma, gumma, helminthic disorders and other granulomatous processes, may mimic neoplasm but are distinguished readily by pathologic study. Since the concept of neoplasm first emerged, regenerating foci appearing in the damaged liver have been mistaken for neoplasm. It has been remarked in the early portion of this chapter that clear distinction between the coarsely nodular cirrhotic liver and hepatoma still may create some confusion. This is not only the case with diffuse hepatic disease but also obtains in relation to isolated and discrete areas of repair as well. In the latter instance the appearance of one or more sharply circumscribed pallid nodules within an otherwise normal liver creates a situation in which it is virtually impossible to distinguish the lesion from metastatic carcinoma by gross inspection alone. The resemblance is so convincing that many have chosen to ignore the connotations of the microscopic examination and have designated this lesion as benign hepatoma, adenoma or hamartoma.[7, 13] Claims of successful excision of hepatoma may well reflect the removal of nodules of this nature.

The lesions present as single or multiple[2, 3, 4] sharply outlined nodules, gray or grayish brown in color, with seeming encapsulation.[10, 13] Usually embedded well within the substance of the liver, they may be in subcapsular location or project from the free surface. Microscopic examination should dispel the suspicion of neoplasm, for the structure is obviously that common to cirrhosis, albeit in localized form. The lobular pattern is distorted, and fibrous trabeculae course through the lesion in irregular fashion. The persistence of inflammation and the presence of disarranged biliary ductules within the mass of functioning parenchymal elements clearly exclude the possibility of hepatoma or other form of neoplasm. Warvi has emphasized the presence of ductules as a feature of prime differential diagnostic value.[120]

To those who have differentiated this lesion sharply there has arisen the all too frequent controversy of nomenclature. Such names as solitary hyperplastic nodule, focal cirrhosis, localized cirrhosis and benign regenerative nodule have been proposed. It is not within the scope of this discussion to defend one or another term. The lesion is not common, and it suffices that the possibility of its existence be recognized when it is encountered at laparotomy. Although of little prognostic import, the possibility exi that in certain instances of hepatoma arisi in a noncirrhotic liver, foci of this natu may represent the points of origin.

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Chapter 22 HEPATIC ABSCESS

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PYOGENIC ABSCESS OF THE LIVER

Although amebic hepatic abscess is encountered frequently, pyogenic abscess of the liver is relatively uncommon. The latter was formerly of great importance because of its association with appendicitis and pylephlebitis, as well as its grave prognosis. By reducing the incidence of these antecedent infections, the use of specific antimicrobial agents has reduced greatly the incidence of pyogenic hepatic abscess. Yet this condition still may present a problem in diagnosis and management.

Incidence

The exact incidence of pyogenic hepatic abscess is not known, because in the many instances in which necropsy is not done, the diagnosis cannot be established with certainty. Prior to 1938 (the beginning of the chemotherapeutic era) the reported postmortem incidence varied from 0.45 to 1.47 per cent,[56, 35] whereas the incidence based on total hospital admissions varied from 0.04 to 0.007 per cent.[47, 35] In 1948 Kinney and Ferrebee[34] reported a postmortem incidence of 0.56 per cent, but the period covered by this report was not recorded. Of 186 cases of hepatic abscess reported by Ochsner and associates,[55, 56] pyogenic abscess constituted only 25 per cent, whereas amebic abscess comprised 75 per cent. However, this incidence of amebic abscess is greater than that reported by others,[47] since the cases occurred in the South where the incidence of amebiasis is about 3 times greater than in the North.

Formerly, pyogenic hepatic abscess was encountered predominantly in male patients in the ratio of 6 to 4,[56] but in recent years the incidence of many of the predisposing conditions has declined so that today this sex difference probably does not exist. For the same reason, the distribution according to age has changed significantly. A reduction in the severity of appendicitis has lowered the incidence of complications associated with that disease, and the previous predominant occurrence of pyogenic abscess of the liver in the third and the fourth decades[16, 56, 58] is now less striking. No racial susceptibility to pyogenic hepatic abscess has been demonstrated.

Etiology

Pyogenic abscess of the liver results from invasion of the liver by pus-producing microorganisms. This may occur by any of several routes.

Extension of Infection from Contiguous Structures. Suppurative cholangitis appears to have supplanted appendicitis as the commonest antecedent focal infection of pyogenic hepatic abscess. In an analysis of 222 pyogenic abscesses of the liver, Kinney and Ferrebee[34] found 22 per cent secondary to obstruction of the common duct. Of 133 abscesses involving both right and left lobes, 37 per cent were secondary to obstruction of the common duct. This apparent increase may be due, in part, to the relative failure of obstructive cholangitis to respond favorably to the antimicrobial agents. On the other hand, appendicitis and other intra-abdominal inflammatory processes respond favorably to these agents so that the incidence of complications, and of hepatic abscess associated with them, has been reduced greatly. Hepatic abscess may result also from cholecystitis, the infection reaching the liver by way of the lymphatic system, by penetration of gallstones, or by direct rupture of the gallbladder itself into the adjacent liver substance. Kinney and Ferrebee[34] also reported 12 instances of hepatic abscess associated with inflammation of the gallbladder. In 7 the abscess was due to metastases, and in 5 it was the result of direct extension. In addition, suppurative processes in the region of the pancreas may extend directly into the liver substance. Gastric or duodenal ulcers may penetrate through the wall of the stomach into the adjacent liver surfaces to produce localized suppurative processes. However, these abscesses are almost always single, generally small and of no clinical significance. Gastroduodenal ulcers may perforate and result in purulent collections about the liver. These abscesses may extend directly to the liver or indirectly by involvement of lymphatic or venous channels.

Infection by Way of the Portal Venous System. Suppurative appendicitis, complicated by portal thrombophlebitis or portal pyemia, was a common antecedent lesion in pyogenic abscess of the liver prior to the advent of the antimicrobial agents. In fact, Ochsner and associates[56] found that hepatic abscess secondary to suppurative appendicitis and pylephlebitis comprised from 10 to 30 per cent of their series of pyogenic hepatic abscesses. Petrén[58] stated that hepatic abscess or suppurative pylephlebitis of the portal vein occurred in from 0.3 to 0.4 per cent of all cases and in at least 5 per cent of all fatal cases of appendicitis. Others have reported incidences ranging from 0.09 to 0.36 per cent.[56] Pyogenic hepatic abscess may result also from infectious processes in other areas drained by the portal venous system. Gastric or duodenal ulceration and diseases of the rectum, the spleen and the pancreas may produce hepatic abscess. In an earlier series[56] lesions in these areas comprised 8.4 per cent of all pyogenic hepatic abscesses. Infectious processes in the subhepatic region, particularly those in the lesser omental bursa, may result in pyogenic hepatic abscess unless surgical drainage is carried out early, for in this region the secondary involvement of splenic and the superior mesenteric veins is possible. Shallow[66] has reported the occurrence of a pyogenic liver abscess secondary to hemorrhagic pa creatitis and pancreatic abscess which ru tured into the splenic vein, thus infecting t portal system. Rarely, hepatic abscess ma occur in infants as the result of extension infection from the umbilicus through ti umbilical veins.

Trauma. Generally, trauma is considere a rare cause of hepatic abscess, although number of cases have been reported in whi injury was a predisposing factor. In t series collected from the Charity Hospit in New Orleans,[56] where a large number injuries are seen, 10.6 per cent of the cas of pyogenic hepatic abscess were seconda to trauma. Hepatic abscess usually resu from penetrating injuries that either we not treated surgically or were drained i properly. Following injury, blood and b accumulate within the area of hepatic inju and infection results either from mic organisms introduced with the injuring age or from micro-organisms already present the hepatic parenchyma. Nonpenetrati crushing injuries also may result in pyoge hepatic abscess. The mechanism is one contusion of the liver substance, permitti growth of micro-organisms which are alwa present within the hepatic parenchyma.

Infection by Way of the Hepatic Arte A limited number of pyogenic abscesses the liver are a result of extension, by w of the hepatic artery, of infection from pr esses elsewhere. These hematogenous inf tions may arise from osteomyelitis, subac bacterial endocarditis, infection of the up respiratory tract, or any other conditi from which septicemia may result. The in dence of pyogenic hepatic abscess result from such infections probably has been duced as a result of early antibiotic cont of most of these infectious processes.

Idiopathic or Cryptogenic Hepatic A scess. Approximately one half of all hepa abscesses have no known predispos cause. Although these are labeled "primar since no distant infectious focal proces can be found, they probably are second abscesses which arise from infection thro one of the aforementioned routes. Roth berg and Linder[62] are of the opinion t such abscesses are the result of hemato nous infections due to distant foci that n

e so inconspicuous as to be overlooked
ompletely. Beaver,[2] on the other hand, has
xpressed the belief that the idiopathic he-
atic abscess is the result of unrecognized
fections in the areas drained by the portal
enous system.

BACTERIOLOGY

Micro-organisms commonly found in pyo-
enic hepatic abscess are colon bacilli, strep-
ococci and staphylococci. In addition, he-
atic abscess due to Friedländer's bacillus
being reported with increasing fre-
uency.[6, 35, 67, 46, 13] In 1940 Boettiger[6] col-
cted 25 cases of hepatic abscess due to
riedländer's bacillus and reported 2 addi-
onal ones. In 1943 Kinney and Ginsberg[35]
ollected 23 such cases and added 7 of their
wn. These authors pointed out that between
896 and 1933 Keefer reported 75 cases of
epatic abscess in over 10,000 autopsies, an
cidence of 0.7 per cent, whereas from 1934
1941 in the same institution there were
2 cases of hepatic abscess, or an incidence
f 0.9 per cent. In Keefer's series, no case of
bscess due to Friedländer's bacillus was re-
orted, whereas in the author's series, 7, or
3 per cent of 30 abscesses in which culture
as performed, were due to this organism.
our instances of hepatic abscess due to
naerobic nonhemolytic streptococci have
een reported.[64, 22, 41, 71] St. John[64] is of the
pinion that if anaerobic culture methods
ere employed more often, anaerobic organ-
ms would be isolated with greater fre-
uency. In several instances abscesses due
Bacteroides funduliformis have been en-
ountered.[63, 3, 26] In many instances hepatic
bscess which occurs without an obvious
rimary cause is due to the *Staphylococcus*
ureus.[30, 19] Frequently, there is a long latent
terval between the original infection, which
often insignificant, and the development
the hepatic abscess. Abscesses due to
coli may contain gas.[76] This organism is
ormally aerobic but is also a facultative
naerobic and gas producer, and the high
ycogen content of the liver appears to be
ideal culture medium for *B. coli*. Pyo-
enic abscess associated with schistosomia-
s[24] and ascariasis[49, 32] also has been re-
orted. Other micro-organisms which rarely
use hepatic abscess are *B. aerogenes capsulatus, B. pyocyaneus,* leptothrix, streptothrix, salmonella, spirochetes, and gonococci.

The purulent material obtained from pyogenic hepatic abscess frequently proves to be sterile when cultured. In about 50 per cent of the cases reported by Elsberg[17] and Rothenberg and Linder[62] and in 40 per cent of the cases reported by Ochsner and associates[55] the pus was sterile.

PATHOGENESIS AND PATHOLOGY

The infrequency with which hepatic abscess occurs is somewhat surprising in view of the liver's direct vascular communications with the portal and the systemic circulations, its intimate biliary system, and its communicating lymphatic channels. That infection is not encountered more commonly is due undoubtedly to the liver's rich blood supply, its characteristic sinusoidal vascular structure with freely moving blood, and the phagocytic reticuloendothelial cells making up the parenchyma. These factors combine to provide a high degree of immunity against localization of infection and the subsequent development of abscess. As pointed out previously, infection by way of the portal and the systemic circulations was the commonest mode of development of pyogenic hepatic abscess prior to the advent of the antibiotic agents; today infection along these routes is rare indeed. However, the biliary system has come to play an increasingly important role in the pathogenesis of hepatic abscess, largely as a result of the relative increase in incidence of hepatic abscess secondary to biliary obstruction and ascending cholangitis. Common duct obstruction may be due to a variety of causes, such as gallstones, inflammatory strictures about the ampulla of Vater or inflammatory or neoplastic diseases of the pancreas. Infection of the biliary system commonly is superimposed upon biliary stasis secondary to common duct obstruction, and the spread of the inflammatory process through the biliary tract and into the substance of the liver follows rapidly. Kinney and Ferrebee[34] noted that 50 of 222 cases of hepatic abscess followed common duct obstruction. When the bile ducts are the route of infection, the distribution of the infectious process corresponds to the architecture of the bile duct system, thus fre-

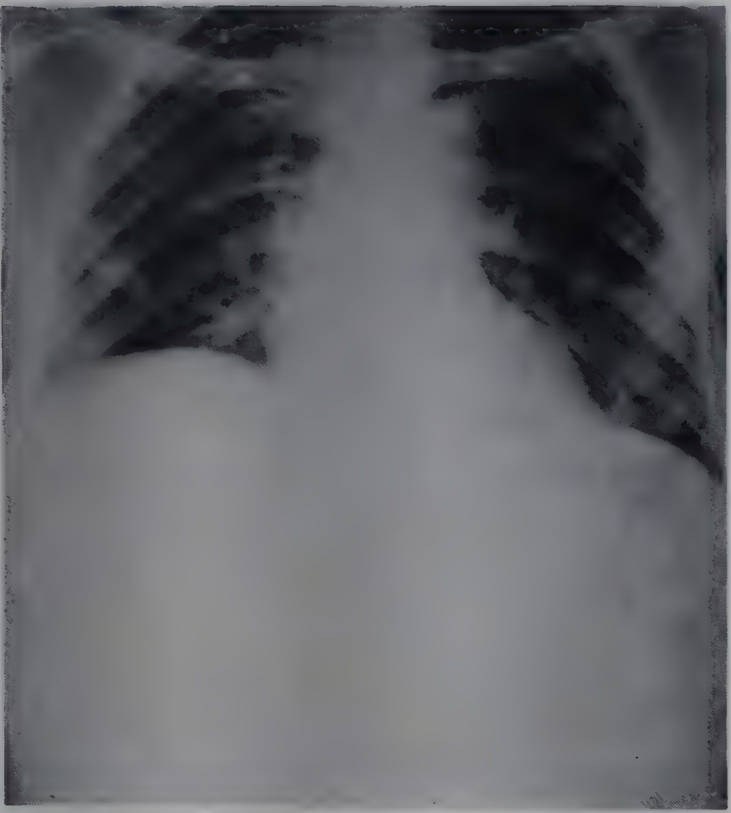


FIG. 174. Roentgenogram of the chest of a patient with carcinoma of the common bile duct. There is elevation of the right leaf of the diaphragm and slight blunting of the cardiophrenic sulcus.

quently resulting in multiple suppurative foci. Periphlebitis may be superimposed on suppurative cholangitis by extension of infection along the portal spaces through the lymphatics or the small veins of the bile ducts. Such a process may result in involvement of almost the entire liver and closely resembles the abscesses resulting from appendicitis and portal pyemia. In cholecystitis associated with cholelithiasis, occasionally the gallstones may penetrate the gallbladder bed and directly involve the liver substance, or the gallbladder may rupture directly into the hepatic parenchyma with development of a localized hepatic abscess.

Although in the older literature acute suppurative appendicitis was considered as the most common antecedent lesion in pyogenic hepatic abscess, its frequency probably was overestimated. Today, with the decline of complications of acute appendicitis, its role in the production of pyogenic hepatic abscess has become even less important. Waller[56] in 1846 reported probably the first instance of appendicitis complicated by multiple hepatic abscesses. Later, Reginald Fitz,[20] in his classic description of appendicitis, mentioned its occurrence. The Fren clinicians, particularly, recognized the portance of appendicitis as an anteced lesion.[12] The proper genesis of this infect is easy to follow. In the course of inflamm tion of the appendix, thrombophlebitis the appendiceal intramural vessels occu The phlebitis can involve progressively appendiceal veins and the meso-append the ileocecal, the superior mesenteric and portal veins, or a small septic embolus become detached from the thrombus in immediate neighborhood of the inflamed pendix and be transported through the c tributing venous channels and the portal v to the liver. The abscesses are usually mu ple and for the most part occupy the ri lobe. The explanation for this latter fact in the experimental work of Sérégé,[65] Gl ard,[25] Bartlett,[1] Copher and Dick,[10] a more recently, Kinney and Ferrebee.[34] Th investigators have demonstrated the ex ence of two currents of blood in the po vein: one from the superior mesenteric v which flows to the right lobe, and one fr the inferior mesenteric and splenic ve which flows to the left lobe.

Other lesions in the portal area may ca pyogenic hepatic abscess by extension infection via the portal route. Infected h orrhoids, proctitis, diverticulitis, bacil dysentery, carcinoma of the colon, and ul ations of the intestinal tract are all poter causes of hepatic abscess. In addition, patic abscess may result from direct ex sion from contiguous suppurative proces Gastric or duodenal ulceration with local abscess formation may extend through hepatic capsule and produce an absces the liver. Infection of the pleural cavity been reported to penetrate the diaphr and invade the substance of the liver.

Direct trauma to the liver, such as pe trating wounds, may give rise to hep suppuration. Injuries that produce the gr est destruction of hepatic tissue are m likely to be followed by infection and scess formation. Blunt trauma to the b wall may also produce injury to the hep tissue, either with contusion with pa chymal hemorrhage and extravasation bile, or with tear of the hepatic capsule fracture of the parenchyma. Then the t

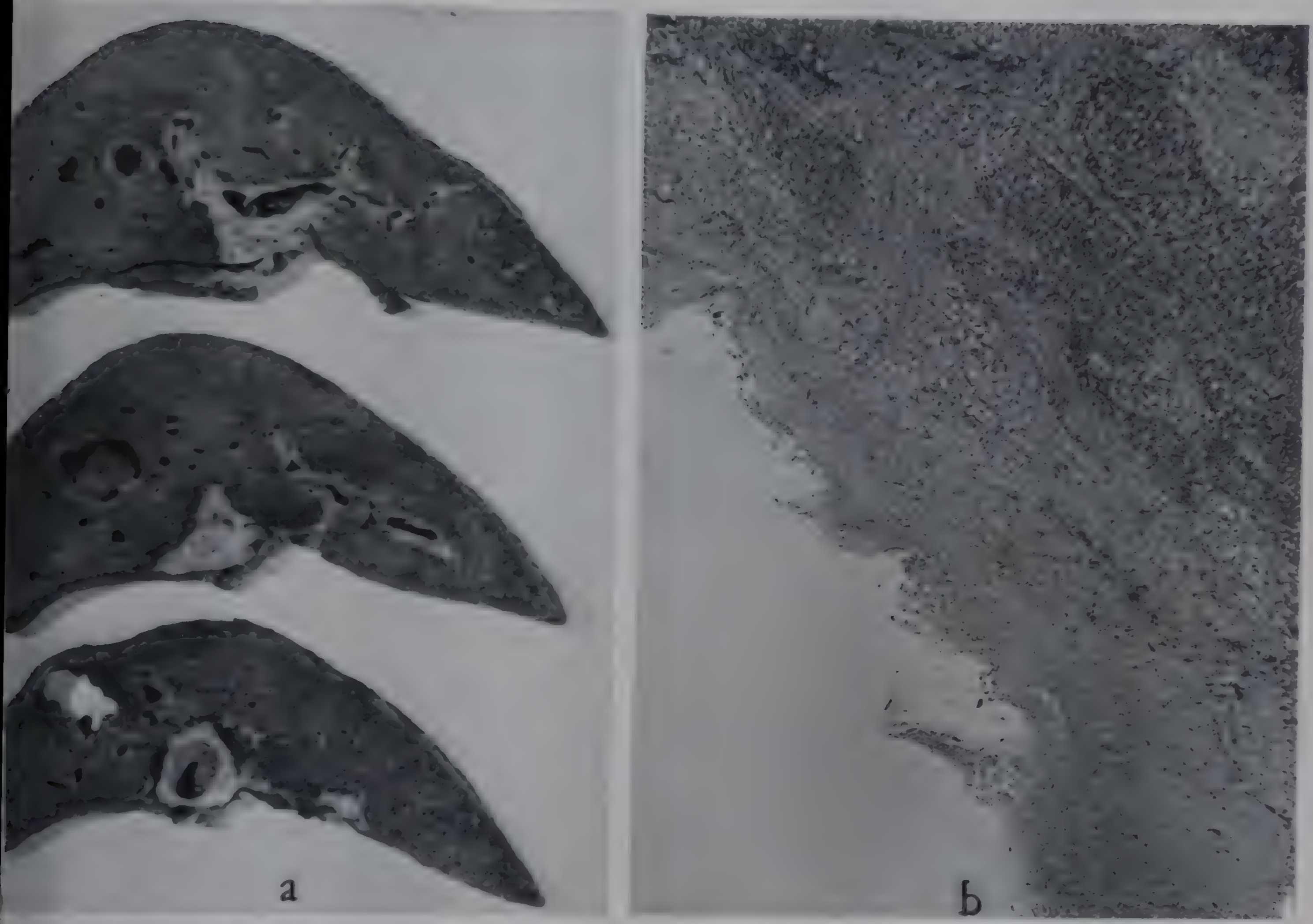


FIG. 175. (a) Postmortem examination of the patient represented in Figure 174 disclosed a large pyogenic abscess occupying the right lobe of the liver and extending toward the diaphragmatic surface. (b) Photomicrograph of section taken from the wall of the abscess. The inner margin of the abscess is composed of cellular debris and infiltrations of leukocytes. More peripherally, fibrous connective tissue and inflammatory cells are interspersed among islands of hepatic cells.

tized portion of the liver may become
aded by pathogenic organisms that are
ays present in the liver substance. The
cesses resulting from trauma are usually
gle and well localized.

Pyogenic hepatic abscess may result also
m penetration of foreign bodies. Lambert
orted a case resulting from passage of a
through the stomach into the right lobe
the liver. Other unusual penetrating for-
n bodies, such as a fishbone, a piece of
ss, a fragment of straw and a toothpick
e been reported.[56, 43]

Hepatic abscesses may be single or multi-
Multiple pyogenic abscesses of the liver
ally result from involvement of the portal
n, the hepatic artery, or the biliary sys-
. Although Ochsner and associates[56]
nd multiple hepatic abscesses in only 45.5
cent of their cases, the increasing incidence of hepatic abscess secondary to ascending cholangitis suggests an increase also in the incidence of multiple hepatic abscesses. Ochsner, De Bakey and Murray[56] reported involvement of the right lobe in 68.1 per cent, of the left lobe in 2.2 per cent, and of both lobes in 27.2 per cent, whereas Kinney and Ferrebee[34] reported an incidence of 32 per cent, 8 per cent and 59 per cent for these respective lobes. It has been suggested that many of the large solitary abscesses begin as multiple small lesions and increase in size and coalesce to form one large abscess cavity.[5] Rothenberg and Linder[62] found that the single abscess occurs 5 times more frequently in the right than in the left lobe and is usually near the dome of the liver. Chronic solitary hepatic abscess with fibrous tissue formation of the wall has been well described by Beaver.[2] In 8 cases reported

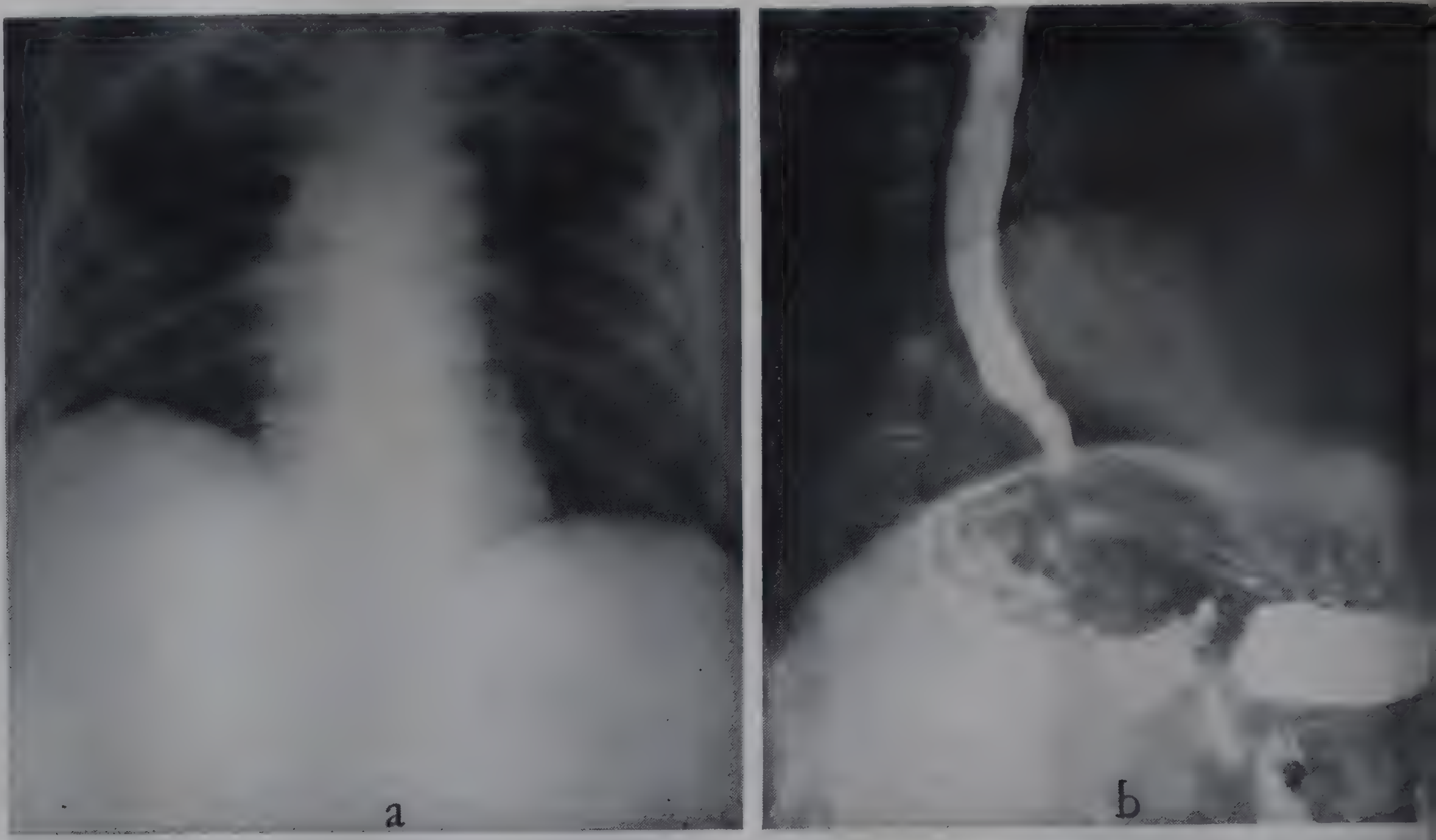


Fig. 176. (a) Postero-anterior roentgenogram of the chest of a patient with carcinoma of the pancreas and cholangitis. The right leaf of the diaphragm is elevated, and there is partial obliteration of the cardiophrenic sulcus. (b) Lateral roentgenogram taken during an upper gastro-intestinal series 1 week later shows marked elevation of the right leaf of the diaphragm, particularly in its anterior portion, with obliteration of the anterior costophrenic sulcus.

by him the abscesses were extremely chronic in nature, varying in duration from 10 months to over 2 years. The granulomatous appearance of these lesions was striking.

In suppurative pylephlebitis the portal vein and its branches are found to contain pus and disintegrated blood clots. Dilatation of the veins, which is due to weakening of the walls of the vessels resulting from the inflammatory process, with subsequent bulging is characteristic. Further involvement of the vessel may lead to perforation, facilitating escape of pus into the surrounding hepatic parenchyma. The extent to which the portal vessels are involved may vary considerably. The liver containing a hepatic abscess is almost invariably enlarged (Figs. 175 and 179a). In some instances its weight is doubled. Because of involvement of Glisson's capsule, perihepatitis is common and occasionally may produce adherence to the diaphragm. Coagulation necrosis precedes suppuration and may give the erroneous impression of multiple metastatic nodules from a distant neoplasm. The organ n
present a mottled appearance, the areas
abscess formation being pale yellow in c
trast with the deep maroon color of
uninvolved hepatic tissue. On section,
abscesses, when multiple, may be seen s
tered throughout the liver substance (
177a), although in some cases they
more or less confined to particular ar
the left lobe escaping involvement more o
than the right. The necrotic areas may v
in size from a fraction of 1 mm. to 1 cm
more. Coalescent small abscesses f
larger cavities, or, in some cases, adja
necrotic areas lend a honeycombed app
ance to the diseased organ. The hep
parenchyma may be destroyed so extensi
as to leave only a shell of the organ.

Microscopically, pylephlebitis is cha
terized by round-cell infiltration of the
nous wall, with leukocytes and cellular de
present in the lumen. Adjacent hepatic c
exhibit reaction to the inflammatory proc
with various stages of degeneration usu

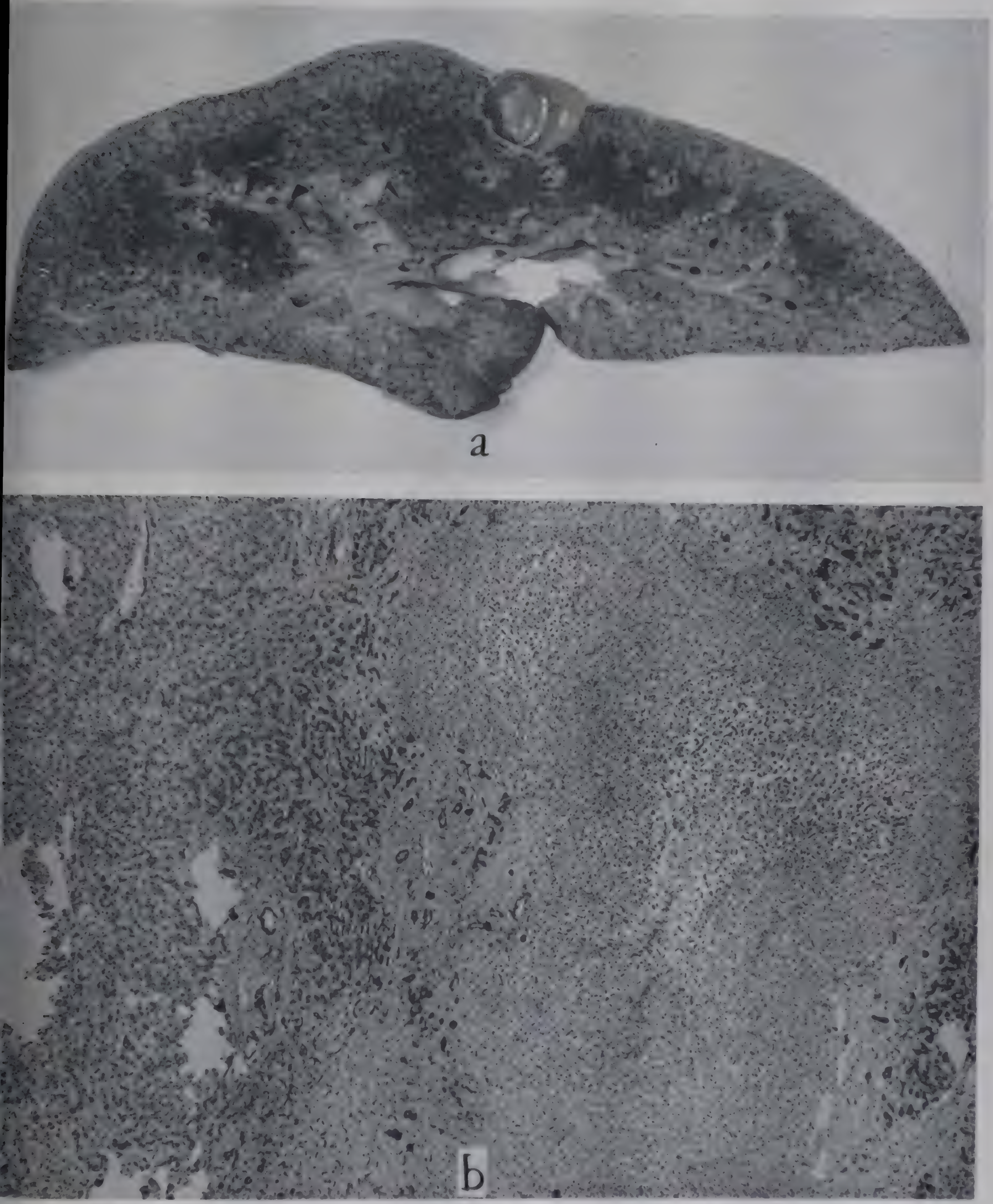


FIG. 177. (a) Postmortem examination of patient represented in Figure 176 disclosed multiple, small cholangitic abscesses throughout the hepatic parenchyma. (b) Photomicrograph of section of hepatic parenchyma containing an abscess. A central area of necrosis is surrounded by leukocytic infiltration. On the periphery, fibrous connective tissue and infiltrations of inflammatory cells are interspersed among hepatic cells.

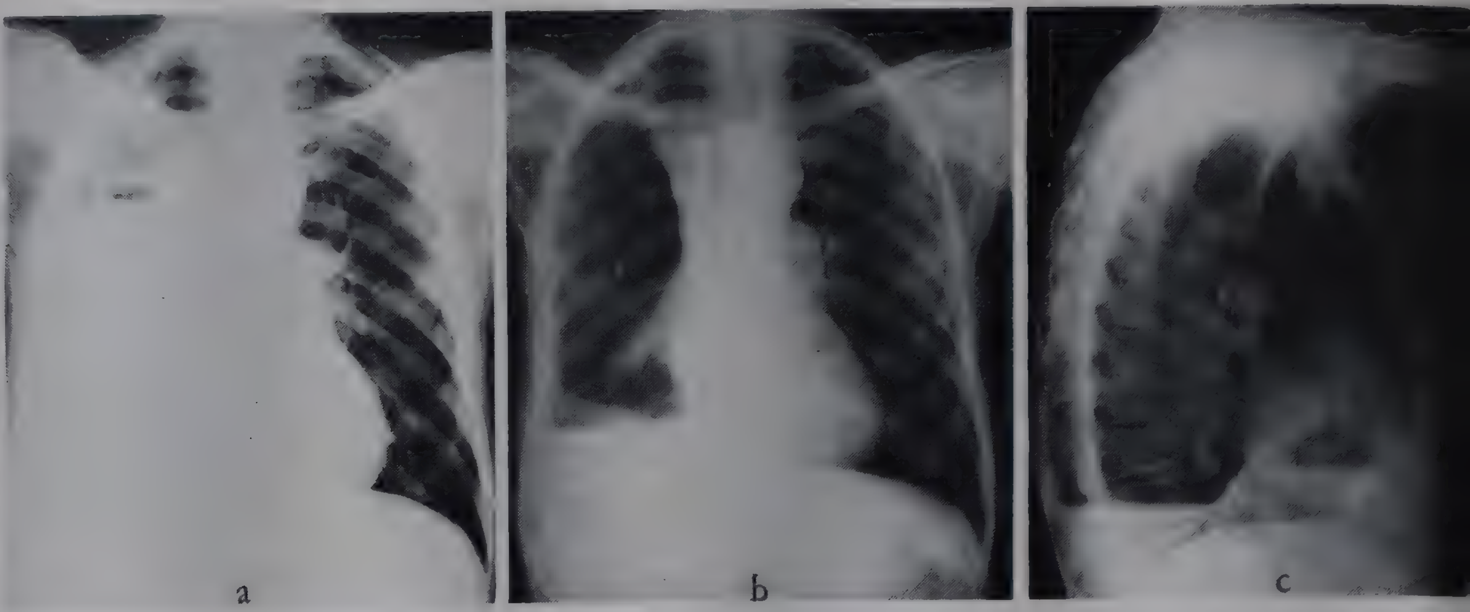


FIG. 178. (a) Postero-anterior roentgenogram of the chest reveals a loculated, right hydrothorax. (b) Following thoracentesis, almost complete collapse of the lung is noted. (c) Right lateral roentgenogram reveals elevation of the anterior portion of the right leaf of the diaphragm with obliteration of the anterior costophrenic sulcus. There is a cavity beneath the diaphragm that appears to extend upward into the chest.

demonstrable. Cellular necrosis characterizes the areas of abscess formation (Fig. 175b). The central portions of the larger lesions contain practically nothing but cellular debris, whereas a fibrous capsule limits the periphery (Fig. 179b). The multiple abscess cavities occurring in suppurative cholangitis usually are filled with bile-stained purulent material (Fig. 177b).

CLINICAL MANIFESTATIONS

Symptoms. The symptoms of pyogenic hepatic abscess may be due primarily to involvement of the liver itself, the systemic response to hepatic sepsis, or the inflammatory process from which the hepatic abscess originated.

Fever is almost always the initial symptom. The temperature may range from 100° to 105° F. Fever may be remittent, intermittent or continuous, depending upon the type of abscess and the pathogenic organisms involved. Characteristically, multiple hepatic abscesses associated with cholangitis, pylephlebitis and suppurative appendicitis give rise to a fever of the "picket fence" type, which is accompanied by daily chills. The solitary pyogenic abscess generally produces a less severe febrile response, and chills occur less frequently (Fig. 181). The occurrence of chills followed by rapid rise of
temperature during the course of appen
citis is strongly suggestive of pylephleb
and hepatic abscess.

Malaise, anorexia, weakness, loss
weight and abdominal distention are co
mon. Nausea and vomiting occur in ab
20 per cent of patients.

Pain, usually dull and constant, is alm
always present but is rarely the initial syn
tom. Rothenberg and Linder[62] found t
patients with single abscesses complained
pain from 1 to 3 weeks after onset of ch
and fever. Pain occurs most commonly o
the hepatic area, either anteriorly in the ri
hypochondrium or epigastrium, or later
in the axillary line. Extension to the ri
shoulder, probably as a result of phre
irritation, has been reported.[14] About 40
cent of Rothenberg and Linder's patie
complained of pain on inspiration in
region of the lower right portion of the ch
probably as a result of involvement of
diaphragmatic pleura. Intercostal pain
development of pleural effusion have b
noted also.

The average duration of symptoms
pends upon the type of onset. About 6
cent of Rothenberg and Linder's patients
symptoms 3 weeks or less prior to hospi
zation, whereas this group constituted
proximately 40 per cent of the cases colle

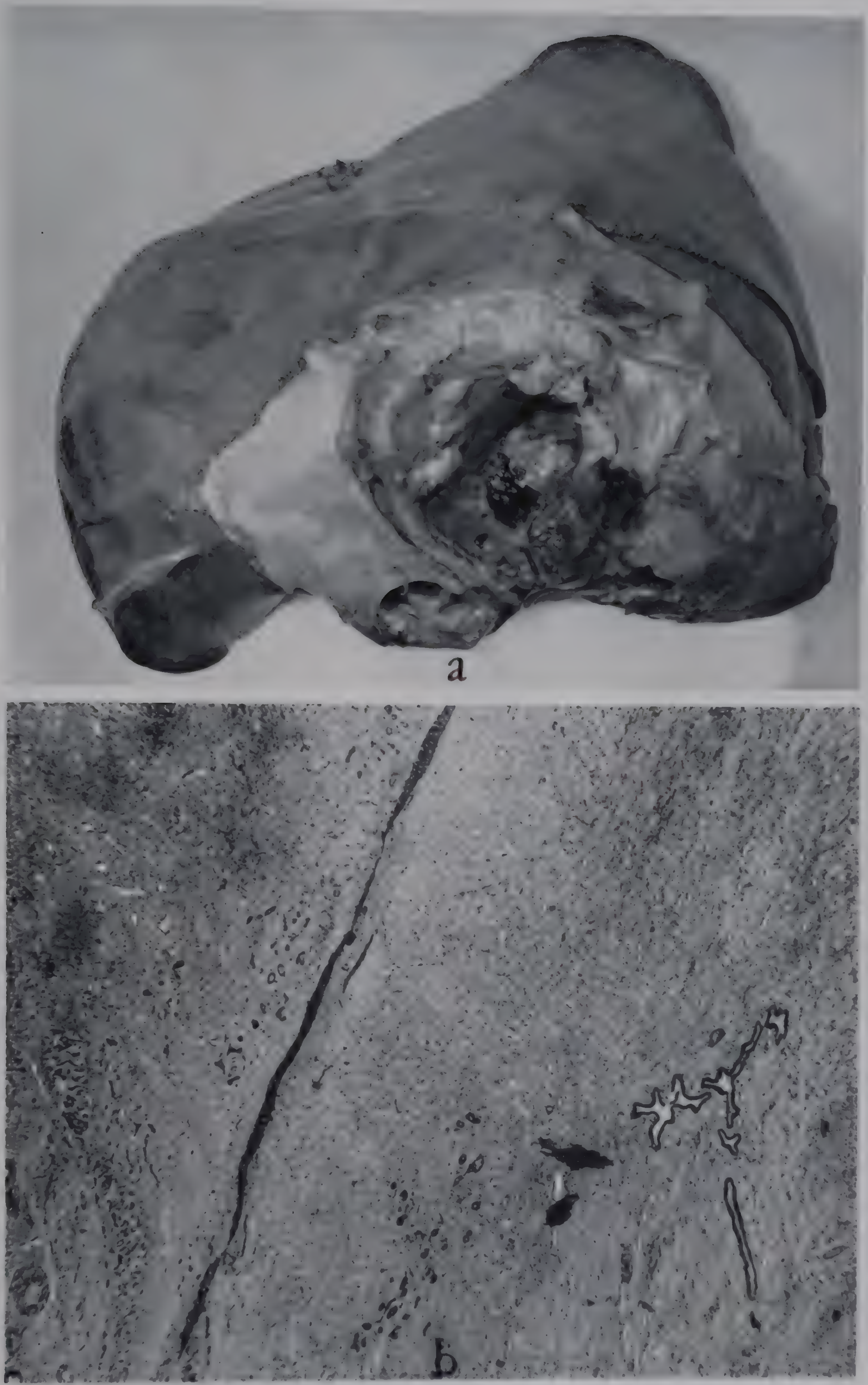


FIG. 179. (a) Postmortem examination of patient represented in Figure 178 disclosed a large abscess in the right lobe of the liver that had extended through the diaphragm and into the right pleural space, producing thoracic empyema. (b) Photomicrograph of section taken from the wall of the abscess. There is extensive infiltration of hepatic parenchyma with fibrous connective tissue, and aggregations of lymphocytes, plasma cells and large mononuclear cells. Islands of hepatic cells and newly formed bile ducts are evident.

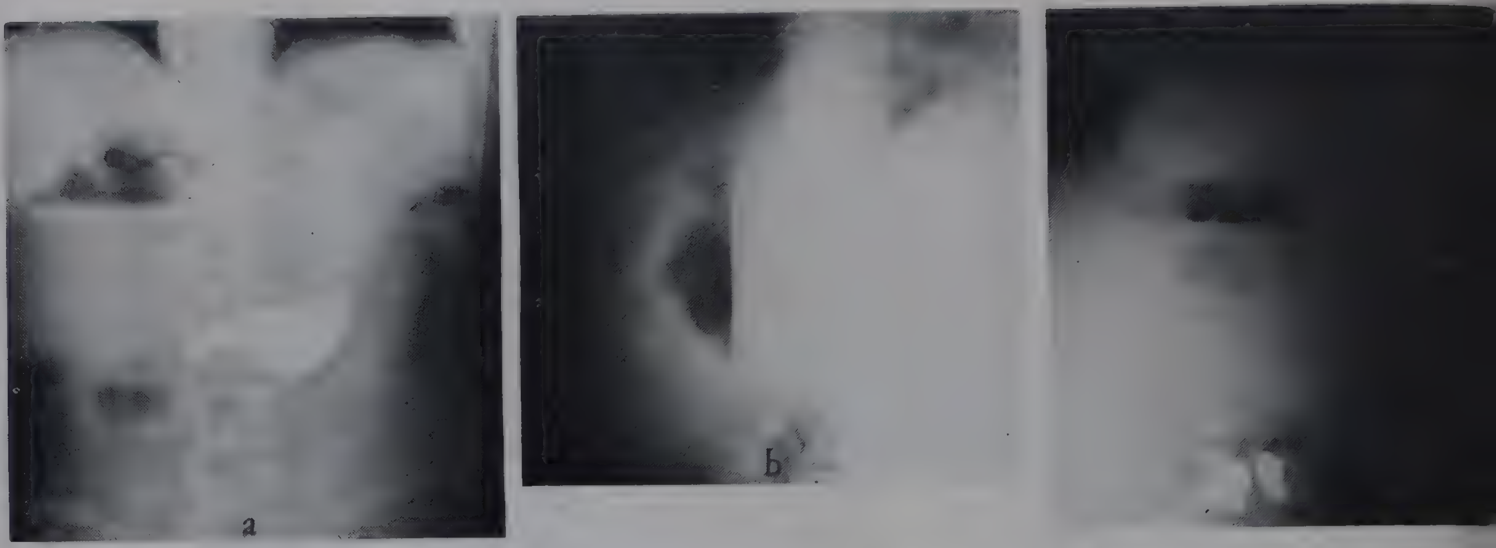
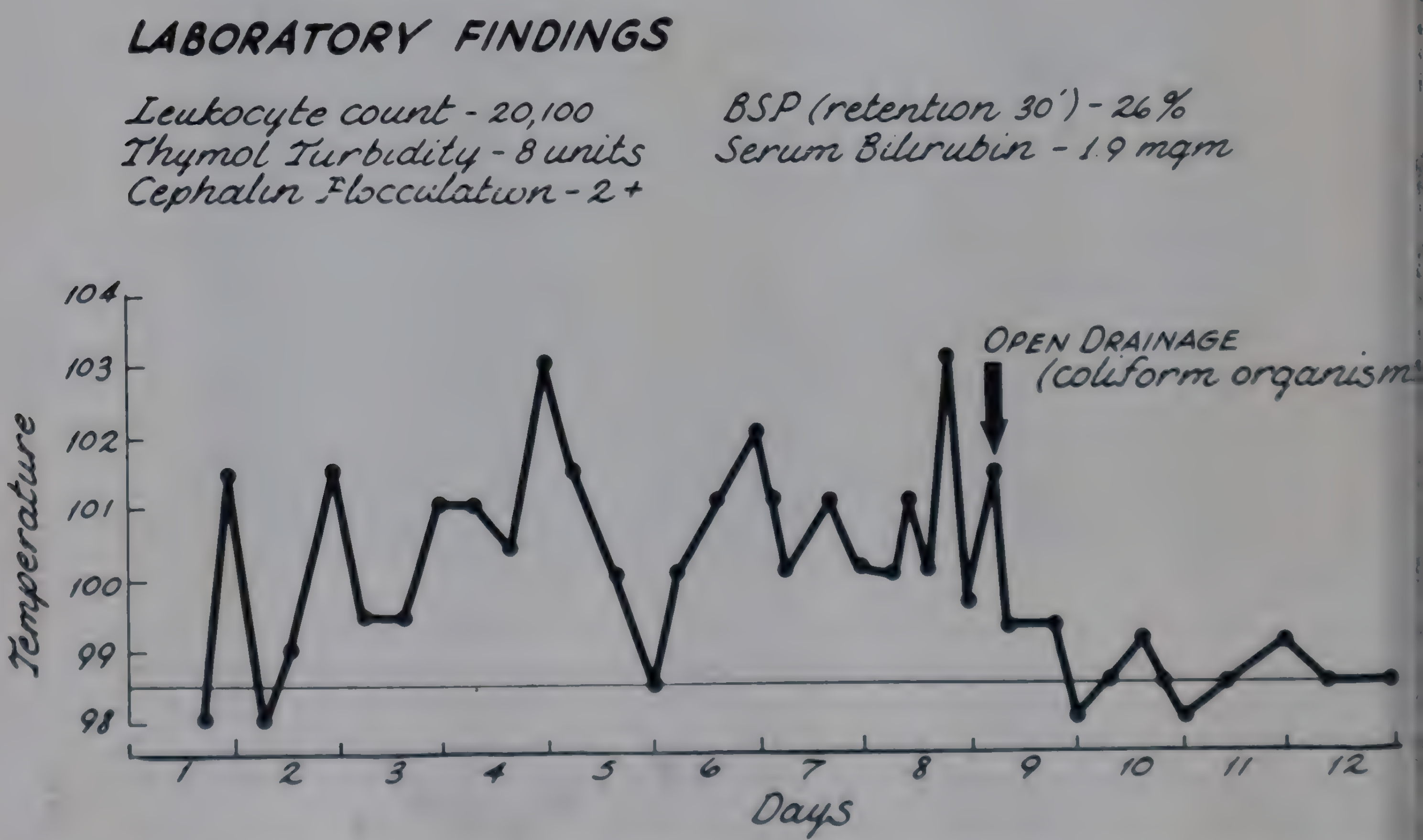


FIG. 180. Roentgenograms of the diaphragmatic region of a 54-year-old patient with vague, upper abdominal symptoms and impaired liver function. (a) Postero-anterior roentgenogram made during upper gastro-intestinal series reveals a gas pocket with fluid level in the region of the right lobe of the liver. (b) With the patient in the lateral decubitus position, the roentgenogram shows the abscess to occupy almost the entire thickness of the right lobe of the liver. (c) Right lateral roentgenogram indicates the anteroposterior extent of the abscess.

by Ochsner and associates,[56] the average duration being 11 days.

Physical Findings. Enlargement of the liver and tenderness in the hepatic area are the most constant physical signs. Hepatomegaly, occurring in either an upward or downward direction, is present in 60 to 9 per cent of patients with pyogenic hepat abscess. This is one of the few conditio producing upward enlargement of the live



LABORATORY FINDINGS

Leukocyte count - 20,100
Thymol Turbidity - 8 units
Cephalin Flocculation - 2 +
BSP (retention 30′) - 26 %
Serum Bilirubin - 1.9 mgm

FIG. 181. Clinical chart of the patient with a large solitary abscess of the liver represented in Figure 180. Following open drainage of the abscess, there was rapid subsidence of symptoms. Culture of purulent material removed during drainage disclosed coliform organisms.

enderness over the hepatic area can be licited in almost all patients with hepatic bscess. Occasionally, the abscess may pro- uce a localized, downward enlargement of he liver that can be palpated below the ostal margin. Infrequently, the skin over- ying the abscess is red and swollen; this ndicates involvement of the abdominal arietes. Jaundice is a common sign of he- atic abscess associated with ascending holangitis and of multiple abscesses of pyle- hlebitic origin but is rare in other types of epatic abscess; when it occurs it is of grave rognostic import.

In the absence of pre-existing hepatic dis- ase, ascites is rare except as a terminal vent. There were no instances of ascites in he cases of Rothenberg and Linder[62] or of Dchsner, De Bakey and Murray.[56] When it loes develop, it is more likely to be in cases f hepatic abscess originating in appendi- itis and suppurative pylephlebitis.

If the abscess projects below the costal nargin, spasm of the muscles in the upper ight quadrant (epigastrium) may be pres- nt, and then the liver border is felt with ifficulty. Tenderness in the intercostal paces is common and usually associated vith limitation of expansion of the right ower portion of the chest. Generally, the atient will prefer to lie on the right side ecause of the splinting effect which this osition affords. In patients with upward nlargement of the liver, there will be in- reased dullness over the right lower portion f the chest, and if the inflammatory process ivolves the diaphragm, rales at the base of ne right lung or signs of pleural effusion nay be elicited.

Laboratory Observations. Pyogenic he- atic abscess is associated characteristically vith leukocytosis, which generally will vary n degree with the acuteness of the suppura- ve process (Fig. 181). An average leuko- yte count of 26,924 cells per cu. mm., with 9 per cent polymorphonuclear leukocytes n the most acute cases, has been reported.[56] n the more chronic cases the leukocyte ount is slightly elevated, and the number of olymorphonuclear leukocytes is also pro- ortionately less. Rothenberg and Linder,[62] n a group of patients with solitary hepatic bscess, found an average leukocyte count of 16,000 cells per cu. mm., with 86 per cent polymorphonuclear leukocytes. In the chronic hepatic abscesses the leukocyte count may be normal. Acute hepatic abscess may be associated with slight anemia, whereas chronic abscesses almost invariably are accompanied by a reduction in the erythrocyte count and hemoglobin.

Urinalysis generally reveals nothing abnormal. In patients with a severe septic course albuminuria may be present, and jaundice usually is associated with bile in the urine. Hirschowitz[29] is of the opinion that excessive amounts of urobilin should be present in the urine, and that normal amounts practically exclude pyogenic hepatic abscess.

Where hepatic abscess results from septicemia, blood cultures will be positive. Gutman and associates[28] noted significant elevation of alkaline phosphatase levels in the blood of patients with multiple hepatic abscesses resulting from ascending cholangitis. Results of other liver-function studies generally are not altered. In fact, rapidly occurring hepatic enlargement in a patient with normal liver function should suggest the presence of hepatic abscess. On the other hand, hepatic abscess occasionally may masquerade as portal cirrhosis.

Roentgenographic Observations. Roentgenographic examination is unquestionably one of the most effective aids in the diagnosis of hepatic abscess. Characteristically, elevation and limitation or absence of motion of the diaphragm, particularly on the right, can be demonstrated fluoroscopically or roentgenographically. These changes have been emphasized by a number of observers.[57, 11, 37] The characteristic changes in contour of the diaphragm in hepatic abscess were first noted by Granger[27] and subsequently emphasized by others.[50, 51, 52, 54, 55, 56] Obliteration of the cardiophrenic angle in the anteroposterior roentgenogram (Figs. 174 and 176a) and obliteration of the anterior costophrenic angle in the lateral view (Figs. 176b and 178c) are characteristic of hepatic abscess associated with subphrenic infection. On the other hand, in subphrenic abscess due to other causes, the anteroposterior view shows obliteration of the costophrenic angle; the lateral view shows obliteration of the posterior costophrenic angle.[48, 53] Abscesses involving the left lobe of the liver may be more difficult to demonstrate roentgenographically, but, as pointed out by Miles,[42] abscesses of the left lobe may produce pressure deformities on the barium-filled stomach in which the lesser curvature assumes a crescentic shape and the cardia and the duodenal cap are displaced. When hepatic abscess is associated with subphrenic infection, pleural effusion is common. Indeed, pulmonary symptoms and roentgenographic signs may be so prominent as to obscure the symptoms and signs pointing to hepatic abscess.

In 40 per cent of the cases of single pyogenic hepatic abscess reported by Rothenberg and Linder,[62] elevation and fixation of the diaphragm were noted, and positive roentgenographic signs were present in 82.1 per cent of the cases studied by Ochsner and associates.[56] When the hepatic infection is due to gas-producing organisms, fluid levels within the liver substance may be demonstrated roentgenographically (Fig. 180).

Roentgenographic examination following aspiration of a hepatic abscess and injection of radiopaque material has been suggested by a number of investigators. Wilmoth[73] employed Lipiodol. Reeves,[61] Yater,[75] Huard,[32] and Carnot[8] advocated injection of thorium dioxide into the cavity. These methods have been employed in order to determine the size, the shape and the position of the abscess. However, it is questionable whether such procedures have practical value in view of the potential hazard of thorium dioxide, and the possibility of contamination of pleural or peritoneal cavity by the aspirating needle. Hepatosplenography in cases of suspected hepatic abscess has been suggested by Meredith and associates,[40] Reeves and Stuck,[60] Koster,[36] and others[18] who contend that it is useful in differentiating between abscess and neoplasm or cyst of the liver. Hepatic abscess is characterized by margins that are not demarcated sharply from the surrounding substance of the liver but are fuzzy and blend gradually with the adjacent liver parenchyma. Metastatic carcinoma or cysts produce areas of lessened density with sharply demarcated borders. A halo of increased density often surrounds the lesions. It has been stated by Ficklen[18] that the use of Thorotrast hepatosplenograph (1) differentiates between single and multiple abscesses, (2) aids as a precise guide to th surgical approach to a hepatic abscess, (3 establishes a diagnosis of pylephlebitis an (4), when negative, points to extrahepati suppuration. However, in view of the potential hazard from radioactivity of thorium and the granuloma formation that may fo low its use, routine employment of Thorotra hepatosplenograph is inadvisable.

DIAGNOSIS

Although the diagnosis of pyogenic hepatic abscess is not difficult if the conditio is kept in mind and if adequate clinica laboratory and roentgenographic examin tions are carried out, frequently it is ma by exclusion and prolonged observation the patient. In a patient with pain and te derness localized in the hepatic area ar with hepatomegaly, associated with chills ar fever, the possibility of pyogenic hepat abscess always should be considered. Pa and tenderness, although usually well loca ized to the right lower portion of the che or the right upper abdominal quadrant, ma be present in the epigastrium or may exten to the right shoulder. Occasionally, pain confined to the lower portion of the che and, in the presence of tenderness in t intercostal spaces and aggravation of pa by deep breathing and coughing, sugge some primary involvement of the respir tory system. In acute cases the leukocy count should be fairly high with predom nance of polymorphonuclear forms. Fluor scopy and roentgenograms of the chest a the abdomen will reveal the characteris changes already described. It is importa that roentgenograms of the chest include t diaphragm and that the patient be in t erect position when the films are made. Bo postero-anterior and right lateral exposur should be made. Nausea and vomiting a encountered not commonly in hepatic a scess, except when they result from an ass ciated intra-abdominal process. In fa absence of nausea and vomiting in the pre ence of clinical manifestations of int abdominal sepsis points to a diagnosis hepatic abscess.

It is of prognostic and therapeutic i

portance to determine the origin of the hepatic suppuration and the number of abscesses. In a patient with a history of suppurative appendicitis, the diagnosis of multiple hepatic abscess associated with pylephlebitis should not be difficult. The preceding suppurative appendicitis, the sudden onset of chills and fever, pain and tenderness extending from the right iliac region up to the hepatic area, the high white blood count and the obvious sepsis constitute a classic clinical picture. Occurrence of chills and fever and pronounced leukocytosis in a patient with biliary obstruction should suggest the development of multiple hepatic abscesses, particularly in the presence of pain and tenderness over the hepatic area. Lesions in the portal area other than acute appendicitis likewise may give rise to multiple hepatic abscesses, and the occurrence of his complication following such lesions as pancreatic and subhepatic abscesses should be kept in mind.

The single pyogenic hepatic abscess generally is associated with an insidious onset, and frequently it is impossible to determine he origin of the infection. Fever and chills are less prominent, and the leukocytic response is less striking. Jaundice is not common in the single pyogenic hepatic abscess unless it reaches a large size. Thus, in general, the solitary hepatic abscess will be nore difficult to diagnose than the multiple acute abscesses.

It is important to differentiate pyogenic hepatic abscess from amebic abscess. This nay be difficult when the pyogenic hepatic abscess is of the solitary type and is somewhat chronic in nature. The onset of the amebic hepatic abscess is usually insidious. The temperature may be elevated slightly or only moderately, chills rarely occur, and the patient does not appear to be ill. The presence of previous diarrhea and the finding of *Endamoeba histolytica* in the stools confirm he diagnosis. Amebic abscesses may become nfected secondarily, in which case they hould be treated as pyogenic abscesses. Aspiration of the liver as a diagnostic procedure probably is unwarranted in pyogenic hepatic abscess. Although with the use of antimicrobial agents this procedure carries ess risk than formerly, in the majority of nstances the diagnosis can be made by other means, and it is preferable to employ needle aspiration only when operative exposure of the liver has been carried out. If proper clinical and roentgenologic examinations are performed, pyogenic hepatic abscess can be diagnosed correctly in from 80 to 90 per cent of cases.

PROGNOSIS

The prognosis of pyogenic hepatic abscess depends upon (1) the number of abscesses, (2) the type of infecting micro-organism, (3) adequacy of drainage, (4) resistance of the host, (5) presence or absence of complications and (6) nature of the antecedent infectious process. Multiple hepatic abscesses carry a graver prognosis than the solitary abscess. Prior to the advent of antibiotic drugs, multiple abscesses, especially those associated with suppurative appendicitis and pylephlebitis, were considered to be almost uniformly fatal, in striking contrast with the prognosis for the solitary abscess, largely because the single abscess usually could be drained adequately.[56] Eliason[15] reported a case fatality rate of 50 per cent in a series of hepatic abscesses following appendicitis, but 58 per cent of these abscesses were solitary. Ochsner and associates[56] reported a fatality rate of 95 per cent for multiple abscess and 37.5 per cent for solitary abscess.

In 1939 Howard[31] collected from the literature 42 cases of hepatic abscess with recovery, of which 11 were multiple. Since then the increasing number of reports of recovery from hepatic abscess suggests that the use of antimicrobial agents has greatly altered the prognosis. This is particularly true of multiple abscesses that cannot be drained properly. To be most effective, the infecting micro-organisms must be identified bacteriologically, and antibiotic sensitivity studies must be made to determine the proper agent for therapy.

Adequate surgical drainage is one of the most effective measures in the treatment of hepatic abscess. When the abscess is solitary and can be localized properly in the liver, drainage usually brings about striking improvement in the condition of the patient and, when combined with appropriate antibiotic therapy, will effect a cure in the majority of instances. When multiple abscesses are present, however, adequate surgical drainage is generally not feasible and, even with the use of antibiotics, the prognosis is not as good.

Within recent years advances in the use of adjuvant therapeutic measures have also played a significant role in the reduction of fatalities from infections. Careful maintenance of proper fluid and electrolyte balances, more liberal use of blood transfusions, and other supportive measures all tend to improve the resistance of the host to infection.

The presence or the absence of complications resulting from hepatic abscess also may affect the prognosis vitally. In a series of 47 cases, Ochsner, De Bakey, and Murray[56] reported a fatality rate of 90.9 per cent of 22 cases with complications as contrasted with 36 per cent of 25 cases without complications.

Finally, the nature of the antecedent infectious process influences the prognosis of hepatic abscess. If the primary infection can be controlled by antibiotic therapy, surgical drainage, or both, the prognosis is generally good. On the other hand, if the primary infection does not respond to these measures, it is unlikely that the hepatic abscess can be treated successfully, particularly if the abscesses are multiple. Infrequently, multiple hepatic abscesses develop because of septicemia which does not respond to antimicrobial therapy. Under these circumstances the hepatic involvement is simply a part of a generalized infectious process, and the prognosis is that of the septicemia. Thus, although the use of antimicrobial drugs has greatly reduced the incidence of pyogenic hepatic abscess and has improved its prognosis, particularly when surgical drainage is feasible, in those instances in which the infecting micro-organisms are resistant to available antibiotics, and in which drainage is not possible, the prognosis still remains grave.

COMPLICATIONS

Complications of pyogenic hepatic abscess may result from rupture or extension into adjacent structures and, when present, add to the gravity of the condition. In a collected series of 258 cases and in 47 cases of their own, Ochsner and associates[56] found the fatality rate to be, respectively, 60.8 per cent and 36 per cent without complications and 90.7 per cent and 90.9 per cent wit complications. The incidence of complications will depend largely upon the extent (the hepatic involvement as well as the location of the abscess. Formerly, the incidenc of complications was about 25 to 30 pe cent.[56, 16] The exact incidence since the introduction of the antibiotic agents is not know but it probably has been lowered signif cantly.

Pleuropulmonary involvement, the mo frequent complication of pyogenic hepat abscess, occurs in 15 to 20 per cent of case It develops either by direct extensic through the diaphragm or by embolism. Th former route is usually responsible for e tension of the infectious process. Pleuropu monary complications are commonly ass ciated with single pyogenic abscess of th liver, except in cases of septicemia, in whic involvement of other organs is likely to occu The solitary abscess most frequently occu in the right lobe of the liver and usually ne the dome. As the abscess cavity enlarges, extends toward the diaphragm, and soon th structure is incorporated into the wall of t abscess. If the abscess enlarges rapidly b fore adherent pleuritis develops, it may ru ture directly into the pleural cavity wi resulting empyema (Fig. 178). On the oth hand, if it enlarges slowly, pleurisy wi adhesions develops simultaneously, and t pleural cavity is obliterated. Thus, in t absence of a free pleural space, the absce ruptures directly into the lung.

Peritonitis may complicate pyogenic h patic abscess as a result either of ruptu of the abscess into the peritoneal cavity or contamination by transperitoneal drainage the abscess. Because of the extremely hi incidence of peritonitis following transpleu or transperitoneal drainage of hepatic a scesses, methods of avoiding contaminati of pleural or peritoneal surfaces were devis with striking reduction in the incidence pleural or peritoneal complications followi drainage.[44, 48, 53, 56]

Pyogenic hepatic abscesses are comp cated by the development of a *subphre abscess* in from 2 to 5 per cent of cas If septicemia is the antecedent infection, sions will be observed in other organs al such as the lungs, the spleen, the kidn nd the brain. Formerly, this type of compliation was reported to occur in about 4 per ent of cases, and the results were invaribly fatal. Within recent years, however, vith the striking improvement in the results f treatment of septicemia it is likely that ome patients with multiple visceral abscesses re now recovering from this formerly fatal ondition.

Rarely, pyogenic hepatic abscess may upture into the pericardium,[56,77] the vena ava,[56] the hepatic vein,[70,83] the thoracic luct[45] or the abdominal wall.[56]

TREATMENT

The treatment of pyogenic hepatic abcess may be considered conveniently under 1) prophylactic and (2) active measures.

Prophylactic Measures. Since pyogenic iepatic abscess is rarely primary, therapeutic neasures directed toward control and eradiation of the common antecedent infection re of great prophylactic value. Formerly, t was considered essential in patients with ppendicitis and preoperative history of chills o examine the appendiceal, the ileocolic, the nferior mesenteric vessels and the portal ein during operation. This would permit letection of thrombosis in these vessels and ts degree of extension, so that appropriate urgical therapy could be instituted and thus revent the possible development of pylehlebitis and multiple hepatic abscesses. In he older medical literature are a number of eports of operations for pylephlebitis occuring either in the preoperative or the postperative period. Evacuation of the infected hrombosed vein was advocated by Gerster[23] s early as 1903. Somewhat later, Wilms[74] uccessfully treated a case by ligation of the eins at the ileocecal angle. In 1913 Braun[7] roposed ligation of the ileocolic vein and eported 2 cases successfully treated in this ay. Melchior[39] in 1928 collected 13 surgially treated cases, 8 of which were done at he time of appendectomy or drainage with o fatalities and 5 at a secondary operation ith 4 deaths. Similarly, Stewart-Wallace[68] btained good results with this type of operaon. He also reported ligation of the superior esenteric vein with successful results in 4 f 6 cases. Others unsuccessfully attempted ligation of the portal vein in patients with pylephlebitis.[4,9]

The necessity for these prophylactic operations has been almost entirely obviated by the routine employment of antimicrobial drugs in the treatment of infectious processes that give rise to pyogenic hepatic abscess. Thus, although at the time of appendectomy there may be evidence of involvement of the appendiceal or ileocolic veins, prompt institution of antibiotic therapy will generally not only prevent dissemination of the infectious process but will eradicate it entirely in most instances.

When suppurative cholangitis exists as a result of obstruction of the extrahepatic biliary ducts, it is imperative to provide biliary drainage to control the infection. Symptoms will rapidly subside in most patients following surgical drainage combined with appropriate antibiotic therapy.

Active Measures. The active treatment of pyogenic hepatic abscess consists in drainage of the abscess, when feasible, and administration of appropriate antibiotic agents (Fig. 181). Surgical drainage is effective primarily in solitary abscesses. In most instances the abscess can be localized from the clinical manifestations and roentgenographic characteristics. Formerly, drainage through an extraserous approach was emphasized in contrast with the transperitoneal or transpleural approaches, which were associated with an extremely high fatality rate. Today, however, there appears to be no increase in morbidity or mortality associated with transperitoneal drainage, which should be employed for abscesses localized in the anterior or antero-inferior surface of the liver. The abdominal cavity is entered through a cutaneous incision made just beneath and parallel with the costal margin. The involved area of the liver is located, and with the adjacent viscera protected by gauze packs, the abscess is opened and evacuated. Similarly, if a pyogenic abscess of the liver is discovered during laparotomy, it should be drained at that time. On the other hand, if there is no evidence of localization of the abscess in the anterior abdominal region, the best method of drainage is by the retroperitoneal approach.[44,53,56] The cutaneous incision is made over the twelfth rib, which is resected subperiosteally, and a transverse incision is made through its bed at the level of the spinous process of the first lumbar vertebra. The retroperitoneal space is entered through this incision between the upper pole of the kidney and the inferior surface of the liver. Then the parietal peritoneum is mobilized from beneath the diaphragm, and the abscess can be completely drained extraserously.

In most instances the cavity created by the abscess will rapidly fill in with granulation tissue following adequate drainage. However, in some cases drainage may persist indefinitely, necessitating closure of the cavity with a flap constructed from the thoracic or the abdominal wall.

At the time of drainage of the abscess, the purulent material should be cultured to identify the infecting micro-organism so that antibiotic sensitivity studies can be carried out. Specific antimicrobial therapy should be instituted within a relatively short time following drainage. Hepatic abscesses located near the lower border of the liver should be excised completely, if possible. This procedure was reported by MacKenzie and Gray,[38] and, more recently, reports of partial hepatectomy for neoplasms[59, 21, 69] suggest that the procedure may be useful in the treatment of some solitary abscesses of the liver.

Multiple hepatic abscesses usually cannot be drained surgically. For this reason, therapy must consist in intensive administration of antibiotics and supportive measures. In many instances the infecting organism can be identified by culture of material from the site of the antecedent infection. In other instances the multiple abscesses may be discovered at laparotomy, and aspiration of one of the abscesses will yield material for culture. Multiple liver abscesses developing as a result of suppurative cholangitis are treated best by drainage of the extrahepatic biliary ducts combined with intensive antimicrobial therapy.

The complications resulting from pyogenic hepatic abscess usually are treated at the same time as the abscess, since the diagnosis of hepatic abscess is made in many instances only after the development of complications. *Thoracic empyema* resulting from rupture of a pyogenic hepatic abscess through
the diaphragm should be drained. Usually
the point of perforation through the dia
phragm can be located at the time of thora
cotomy, and the location of the absces
within the liver can be ascertained. Follow
ing evacuation of the pleural space and de
cortication of the pulmonary surfaces, th
opening in the diaphragm is repaired if nec
essary. The thoracotomy wound is close
and the chest is drained by an intercosta
catheter connected to a water-seal suctio
bottle. Then the hepatic abscess is draine
usually through a separate incision, depend
ing upon its location. If thoracic empyema i
due to lymphatic extension of the infectiou
process across the diaphragm from the live
it is necessary only to drain the empyem
and to re-expand the lung. The hepatic a
scess is treated separately by drainage a
teriorly or posteriorly. *Bronchohepatic fistul*
usually requires no therapy other than a
ministration of appropriate antibiotic drug
for the abscess cavity may be evacuate
completely through the bronchial fistul
Persistence of symptoms following develo
ment of a bronchohepatic fistula is indicati
of inadequate drainage. Under these circu
stances the hepatic abscess should be draine
surgically. *Pyogenic pulmonary abscess* se
ondary to pyogenic hepatic abscess is ma
aged conservatively. Abscesses not respon
ing favorably to this type of therapy may r
quire resection. *Subphrenic abscesses* can
drained simultaneously with a hepatic a
scess. This is accomplished best by t
extraserous route, either anteriorly or po
teriorly. Peritonitis resulting from ruptu
of a pyogenic hepatic abscess is treated
drainage of the hepatic abscess and evacu
tion of the purulent material from the pe
toneal cavity at laparotomy followed
intensive antibiotic therapy.

HEPATIC AMEBIASIS

Formerly, amebiasis was believed to occ
principally in tropical or subtropical loca
ties. For this reason, amebic abscess of t
liver commonly was called tropical absce
and the nonamebic variety, due to pyoge
organisms, was called nontropical absce
Within the past 2 decades this concept h
proved to be erroneous, since amebiasis h

been detected in many of the northern, eastern and western localities of the United States. In Craig's[15] series of 49,336 persons examined in all parts of the United States, 5,720 (11.6%) were infected with *Endamoeba histolytica.* In examining 189 physicians from all parts of the United States, Craig[15] found *E. histolytica* in 12.7 per cent. Thus, amebiasis unquestionably occurs with significant frequency in all parts of the United States.

The most common site of extra-intestinal amebiasis is the liver. Amebic involvement of the liver may occur as a presuppurative stage, referred to as amebic hepatitis, and also as frank suppuration, which is designated as amebic hepatic abscess.

INCIDENCE

The incidence of hepatic involvement varies considerably, depending upon the incidence and the relative control of the primary ntestinal infection and the nature of the population from which the statistical material is derived. Studies based upon autopsy material show a much higher incidence of hepatic involvement than analyses based on clinical material alone. This is due largely to the fact that cases in which autopsy is performed represent a more advanced stage of the disease. The incidence based on autopsy cases varies from 7.6 per cent to 4.4 per cent, with an average of 36.6 per cent.[17] In clinical cases of intestinal amebiasis the incidence varies from less than 1 per cent to more than 25 per cent, with an average incidence of 8.1 per cent.[17] During the past decade the incidence of hepatic involvement in intestinal amebiasis has shown decrease in spite of an increase in the incidence of intestinal amebiasis. This suggests hat now intestinal amebiasis is being recognized earlier and treated more effectively.

Amebic hepatic infection occurs predominantly in the male sex in a ratio of about to 2. It is observed more frequently during adult life, the highest incidence occurring n patients in the third, the fourth and the ifth decades of life. Rarely is the disease encountered in patients at the two extremes of life. Although all races are susceptible to nfection with *Endamoeba histolytica,* observers in the tropics are of the opinion that clinical manifestations of the disease appear less often in natives than in individuals of the white race in these same areas. Europeans are believed to be more susceptible to development of amebic hepatic abscess than natives of the tropics. Craig[15] believes that these natives possess partial immunity to *E. histolytica,* which is acquired from constant reinfections since childhood, and that this accounts for the comparative mildness of symptoms of amebiasis and relative infrequency of hepatic complications in this group. No predisposition to the white or the Negro races has been demonstrated.

PATHOGENESIS

It is generally agreed that amebas usually gain entrance into the liver by way of the portal system. In support of this hypothesis is the frequent observation of amebas in the capillaries and the venules of the intestinal submucosa and muscularis and in the portal tributaries of sections taken from patients with amebiasis. Two other possible routes of invasion of the liver are (1) direct extension through the intestinal wall, the peritoneum and the capsule of the liver and (2) the lymphatic system. However, it is unlikely that amebas enter the liver to any significant degree by other than the portal route.

Amebas probably are carried to the liver more frequently than is indicated by the incidence of amebic hepatic infection, for as Faust[20, 21] has shown, the hepatic parenchyma appears to possess an amebostatic factor. Actual invasion and growth of amebas in the liver are more likely if an overwhelming number of parasites with relatively increased virulence gain entrance to the liver, or if the resistance of the liver is lowered. The two most significant factors in actual development of amebic hepatitis and amebic hepatic abscess are (1) production by the amebas of intrahepatic portal thrombosis and infarction, and (2) cytolytic activity of the amebas. Amebas carried to the liver from the intestine via the portal circulation are filtered into the portal capillaries, and if they lodge in these smaller portal radicles in sufficient number, thrombosis with infarction and consequent focal necrosis may ensue. Thus, the way is paved for the cyto-

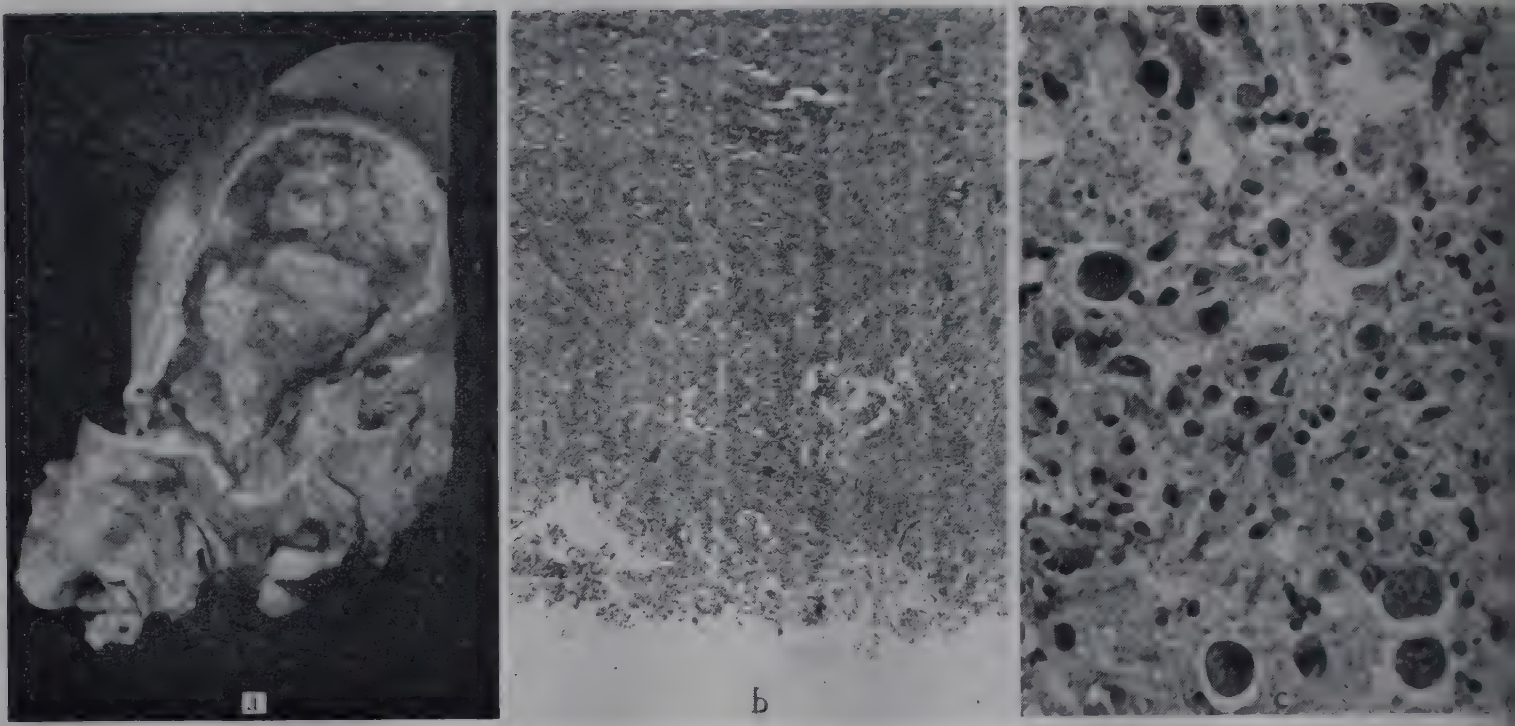


Fig. 182. (a) Photograph of the right lobe of a liver removed at necropsy. An abscess cavity measuring 15 by 10 cm. fills almost the entire lobe. The wall of the abscess is about 1 cm. thick. (b) Low-power photomicrograph of section taken from the wall of the abscess reveals a central zone of necrosis, a middle zone of destroyed hepatic cells in which only a fibrous connective-tissue stroma remains, and an outer zone of hepatic parenchyma which is infiltrated with inflammatory cells. (c) High-power photomicrograph of the section shown in (b) reveals *E. histolytica* in the middle and the outer zones of the abscess wall.

lytic activity of the ameba, permitting lysis and destruction of the involved hepatic parenchyma at the earliest stage of abscess formation. Histologic studies of sections of the liver in various stages provide further evidence of this mode of development of amebic infection of the liver. In the early stage of the process Craig[15] described a peripheral zone of hyperemia surrounding an "area composed of cytolysed tissue cells in which may be seen red blood corpuscles, degenerated liver cells, a few leukocytes, connective tissue cells, and granular debris, with now and then a trophozoite of *Endamoeba histolytica* lying in a zone of completely cytolysed material." This early stage, without progressing any further, may heal by connective-tissue replacement, leaving focal areas of scar tissue representing healed small amebic abscesses. Thus, in the early phase a balance exists between progression of the process toward suppuration and true abscess formation or regression toward healing. The direction in which the infectious process proceeds is determined by a number of factors, including the virulence and th number of the organisms, the resistance c the host, the presence of pathogenic bacteria, and possibly detrimental factors, suc as alcohol and trauma.

Pathology

The gross and microscopic appearance of the liver infected with amebas depen upon the extent and the stage of involvement. Characteristically, abscesses are sing and occur in the right lobe near the dom of the liver or on the inferior surface nea the hepatic flexure of the colon (Fig. 182a Multiple abscesses are encountered occa sionally. It appears that involvement of th left lobe and the presence of multiple al scesses are more common when the disea is far advanced. This is borne out by th highest incidence of left-lobe involvemen and multiple lesions in series based c autopsy cases.[17, 41] Obviously, extensive h patic involvement is more likely in fat cases in which necropsy is performed. Mor over, in clinical cases, small abscesses m esolve with appropriate therapy and remain nrecognized, whereas thorough postmortem xamination will reveal these small lesions.

During the earlier stages of amebic hepatitis amebas are found most frequently in he focal area of necrosis. As the process levelops into true abscesses, the amebas become less evident and are more likely to be ound in the zone of necrotic tissue surounding the peripheral margins of the abcess. Microscopically, there are 3 zones in he active abscess: (1) an outer zone of elatively normal tissue that is being invaded by the amebas; (2) a middle zone in which he parenchymal cells have been destroyed nd only the stroma remains; and (3) the ecrotic center (Fig. 182b). The fact that mebas appear in the peripheral margins of he abscess accounts for the difficulty in lemonstrating them in the "pus" in no more han one third of the cases (Fig. 182c). Amebic hepatic abscess is also typically terile, as shown by the fact that pathogenic organisms can be demonstrated in the purulent material in only a small number of cases, n which instances the organisms are probably secondary invaders. However, when an amebic hepatic abscess becomes infected secondarily the process assumes a pyogenic nature. There is also a change in the appearance of the contents of the abscess. The ypical sterile amebic hepatic abscess contains a viscid, glary, yellowish-red to chocolate-brown material that resembles anchovy sauce or chocolate sauce. Its appearance is so characteristic that it may be considered as pathognomonic. However, once the lesion becomes infected secondarily, the contents become more purulent and have a grayish or grayish-yellow creamy ppearance.

CLINICAL MANIFESTATIONS

The clinical manifestations of amebic hepatic disease are extremely variable. Symptoms may occur suddenly or develop insidiously. They may appear during the acute phase of intestinal amebiasis or months or even years later. They may develop also in patients who never have had dysenteric symptoms, a fact which is not sufficiently nderstood. The erroneous impression still exists that diarrhea is a common or accompanying manifestation of amebic hepatitis and hepatic abscess. However, experience has demonstrated that a relatively large proportion of patients will give no history of diarrhea. In fact, diarrhea or dysentery is a symptom at the time of admission in only one half of the patients with amebic hepatic disease, this symptom occurring with about equal frequency among patients with hepatitis and hepatic abscess.[17, 38 41, 42, 48]

Although the nature of onset and the duration of symptoms in amebic hepatic disease may vary considerably, usually it is possible to distinguish between acute and chronic forms. It is particularly important to recognize the early stage of amebic hepatitis, since institution of appropriate therapy during this presuppurative period may prevent progression to abscess formation. In the acute form of the disease the clinical picture is usually more characteristic, with distinctive manifestations that develop more rapidly than in the chronic form. In about one third of the cases the onset of symptoms is acute (3 weeks or less).

The clinical manifestations of hepatic amebiasis may be classified into systemic and local. Systemic symptoms, in order of frequency, are fever, loss of weight, weakness, profuse chills and sweating, nausea, malaise and anorexia. Although fever is usually of a low grade, intermittent or remittent nature, it may vary considerably, depending upon the onset and the occurrence of secondary infection or other complications. It is present almost invariably in the presuppurative form of the disease, whereas in the later stage of abscess formation it may be absent or of low grade. Chills and sweating also are encountered more frequently in the acute and the subacute forms and in abscesses associated with secondary infection. Weakness and loss of weight may appear early but are more prominent in advanced cases, whereas anorexia, nausea and vomiting are more likely to occur in the early stages of the disease. Although pallor is not uncommon, especially in patients with the chronic form of the disease, jaundice occurs in a relatively small proportion of patients. When present, jaundice is more likely to be associated with abscess formation than with

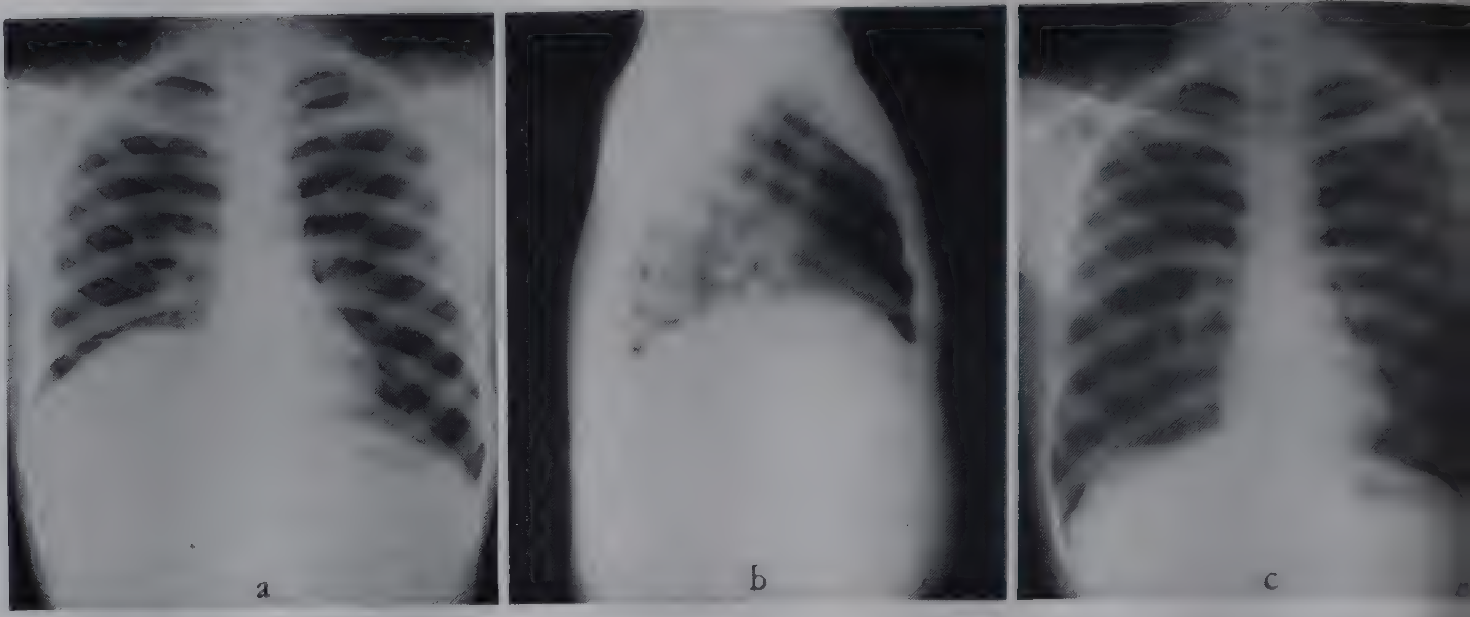


FIG. 183. (a) Postero-anterior roentgenogram of patient with an amebic hepatic abscess, showing elevation of the right leaf of the diaphragm and obliteration of the right cardiophrenic sulcus. (b) Lateral roentgenogram showing elevation of the right diaphragm in its central and anterior portions with blunting of the anterior costophrenic sulcus. (c) Postero-anterior roentgenogram made after aspiration of amebic hepatic abscess. The diaphragm has assumed its normal position, and only a stringlike adhesion remains as a residual of the hepatic abscess.

amebic hepatitis. The earliest and most common local manifestations of hepatic amebiasis are pain and tenderness in the right upper abdominal quadrant in the region of the liver. Pain is variable in nature, ranging from a dull, aching discomfort to a sharp, stabbing pain. Although it usually is located directly over the liver, it may be more severe anteriorly below the right costal margin, in the epigastrium, in the axillary line, or posteriorly over the twelfth rib. At times the pain is pleuritic in type, more prominent in the right lower pulmonary area and accentuated by deep breathing. On the other hand, it may be referred to the right shoulder. Pain in the chest and the shoulder is more likely to be encountered in patients with amebic hepatic abscess than in those with amebic hepatitis.

Enlargement of the liver is another characteristic local sign which is present in over three fourths of the patients. Usually the liver margin can be felt readily below the right costal arch anteriorly, and on percussion liver dullness will be found to extend higher than normal. Palpation of the liver margin may be difficult in some instances because of the acute tenderness and the rigidity of the abdominal muscles in the right upper quadrant. Manifestations of low pl
ropulmonary involvement on the right si
are not uncommon and result from co
pression of the lower portion of the ri
lung as well as from contiguous inflamm
tory changes. Thus, dullness, diminish
breath sounds, crepitant rales, friction r
and signs of fluid in the pleural cavity m
be elicited in the patient with amebic hepa
abscess.

In the chronic form of the disease, sym
toms may develop so insidiously as to
almost unrecognizable. Most patients w
complain only of slight malaise and an
rexia, with no symptoms referable to the
patic area. Only by careful examination
one able to elicit tenderness in the right
dominal quadrant or the lower portion
the right chest, and hepatic enlargement

LABORATORY FINDINGS

Hematologic studies and fecal exami
tion may yield information of diagnostic s
nificance. Characteristically, there is m
erate leukocytosis in amebic and hep
abscess in contrast with the pronoun
leukocytosis occurring in the pyogenic fo
of hepatic disease. Furthermore, in ame
hepatic abscess there is, as a rule, no c

mitant increase in the polymorphonuclear ukocytes. In the acute form of the disease e leukocyte count averages about 16,000 r cu. mm., whereas in the chronic form it about 13,000, with average polymorpho-uclear percentages in these two forms of bout 80 and 75, respectively.[17] In general, ronounced leukocytosis is suggestive of condary infection. Furthermore, the total ukocyte count is greater in hepatic abscess an in amebic hepatitis, and anemia is more ronounced in the former.

As emphasized previously, only about one half of the patients with amebic hepatic disease have associated dysentery, and even with the most careful laboratory examination only about 45 per cent of patients show evidence of amebas or cysts in the stools. Frequent examinations yield positive results in a higher percentage of patients with amebic hepatitis than with amebic hepatic abscess.[52, 53] Thus, De Bakey and Ochsner[17] reported demonstration of amebas in the stools of 66 per cent of patients with amebic hepatitis and in only 47 per cent of those with amebic hepatic abscess.

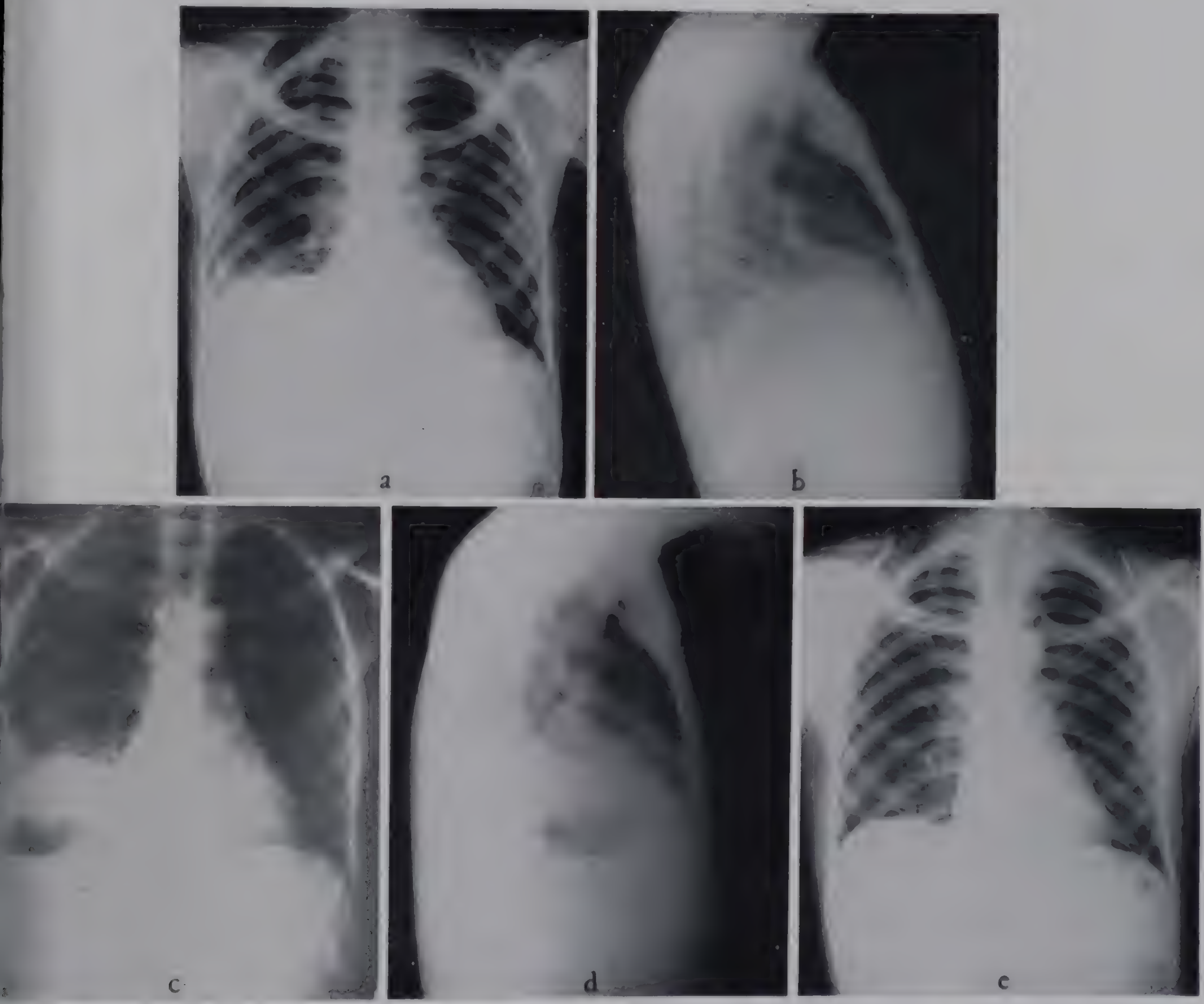


FIG. 184. Roentgenogram of the chest of a patient with an amebic hepatic abscess treated successfully by aspiration. (a) Postero-anterior view shows elevation of the right leaf of the diaphragm with blunting of both costophrenic and cardiophrenic sulci. There is evidence of a basal pneumonitis and pleural effusion. (b) Lateral view discloses elevation of the central portion of the diaphragm with slight blunting of the anterior costophrenic sulcus. (c and d) Following aspiration of the hepatic abscess, air was injected to outline the extent of the cavity. (e) Postero-anterior roentgenogram taken about 1 month after aspiration of the amebic hepatic abscess. The diaphragmatic contour now appears normal.

The specific complement-fixation test, first described by Craig[14] in 1927, is another important diagnostic laboratory procedure. Because of its high degree of specificity it is particularly useful in questionable cases of amebiasis, especially amebic hepatitis and hepatic abscess.[44, 56] The test is similar to the standard complement-fixation test for syphilis; but, unfortunately, certain technical difficulties encountered in preparation of a potent antigen and proper performance of the test have hindered its routine use. The material for performance of the test is not available in most laboratories. Terry and Bozicevich[56] are of the opinion that the complement-fixation test is far more reliable than a history of diarrhea, amebas in the stools, proctoscopic examination, or even a combination of these, in the presence of a clinical picture consistent with hepatic amebiasis. They also believed that it has prognostic value in determining response to therapy, as previously indicated by Craig. On the basis of investigations on 54 patients with amebiasis, 10 of whom had hepatic involvement, Montero and Uribe[35] reached similar conclusions.

Complete liver function studies should be performed on all patients suspected of having amebic hepatic disease. Rarely are these functions altered significantly. They are of value chiefly in differentiation of other types of hepatic disorders. Characteristically, significant enlargement of the liver with normal liver function is suggestive of amebic hepatic disease. However, in some instances, particularly in the presence of liver abscess involving a large part of the hepatic parenchyma, changes in hepatic functions may be observed. Chakravarti,[8] who studied the plasma proteins in 11 patients with amebic hepatitis and 3 with amebic hepatic abscess, noted that in all the albumin level was decreased and the globulin fraction increased, while the total protein level remained within normal limits. The changes were greatest in patients with abscess, and in every instance the plasma protein returned to normal levels following recovery. Hare and Ritchey[23] reported an instance of amebic hepatic abscess which, on the basis of clinical manifestations and laboratory observations, appeared to be portal cirrhosis. In this instance all liver-function values were d
pressed, and only at necropsy was the diag
nosis of amebic hepatic abscess establishe

ROENTGENOGRAPHIC FINDINGS

Roentgenography is a particularly usef
diagnostic procedure in amebic hepatic i
fections.[17, 38, 41, 42] Fluoroscopic examin
tion usually reveals elevation and immob
ity or restriction of motion of the right le
of the diaphragm. Varying degrees of pu
monary and pleural reaction may be o
served in the right basal area, since the po
tion of the liver most frequently involved
the area near the dome, which is in clo
contact with the diaphragm. In addition,
the presence of amebic hepatic abscess,
distinct bulging of the diaphragm upwa
into the lower pulmonary field may
observed.

Roentgenographic examination is pa
ticularly useful in differentiating ameb
infections of the liver and the subphren
space from those due to other causes.[40] T
most common site of pyogenic infections
the subphrenic space is the right poster
superior space, whereas amebic infectio
are located generally in the right lobe of t
liver and near the dome, somewhat mo
anteriorly than posteriorly. Therefore, in t
latter the roentgenogram characteristical
shows, in the anteroposterior view, elevati
of the medial portion of the right leaf of t
diaphragm with obliteration of the cardi
phrenic angle (Fig. 183a and 184a). In t
lateral roentgenogram, elevation is primari
anterior with a tendency toward obliterati
of the anterior costophrenic angle (Fi
183b and 184b). On the other hand,
pyogenic subphrenic infections, there is e
vation particularly of the lateral portion
the diaphragm in the anteroposterior roen
genogram and obliteration of the cost
phrenic angle in the lateral roentgenogra
In amebic abscess of the left lobe of the liv
these observations usually are not appare
and the presence of this type of ame
hepatic infection is difficult to demonstra
in ordinary roentgenograms. However,
has been shown that abscesses in the l
lobe produce characteristic pressure d
formities on the stomach, which may
demonstrated following ingestion of b

um.[34] The cardia, the lesser curvature and he duodenal cap are displaced downward, nd the lesser curvature assumes a typical rescentic shape. The great value of roentgenography in establishing the diagnosis of epatic amebiasis has been demonstrated epeatedly by many observers. The findings f De Bakey and Ochsner[17] are particularly triking in this regard, for of 225 cases of mebic hepatic disease 181 (80.5%) had ositive roentgenographic observations. For bvious reasons, the incidence of positive oentgenologic signs is much higher in hepatic abscess than in hepatitis.

Various modifications in technic have een proposed as an aid in the roentgenographic diagnosis of hepatic abscess. These nclude injection of air (Fig. 184c and d) r iodized oil into the abscess cavity following aspiration[7, 13, 26, 57, 60] and hepatography y means of thorium dioxide[47, 59] and after neumoperitoneum.[28] However, these procedures are of doubtful value, as in the majority of cases the ordinary roentgenographic nethods, together with other diagnostic riteria, are adequate. Furthermore, these pecial roentgenographic technics are an dded risk to the patient. Although in an ccasional case they may be of diagnostic or nvestigational value, they should not be mployed routinely.

DIAGNOSIS

The diagnosis of amebic hepatic infection is made with relative ease once the condition is suspected. However, a high index f suspicion must be maintained in all patients with symptoms localized to the hepatic rea which have no other obvious explanation. Moreover, it must be kept in mind that mebic hepatitis and hepatic abscess frequently develop in patients who never have ad dysenteric symptoms. In addition, the nset may vary considerably. Characteristically, symptoms consisting of low-grade ever, slight to moderate loss of weight, nalaise, anorexia, and pain and tenderness n the right upper quadrant of the abdomen re suggestive of amebic hepatic disease. If he pain has a pleuritic or diaphragmatic omponent, the diagnosis is even more kely. Because of the frequency with which ain occurs in the lower pulmonary area, many cases of amebic hepatic disease are diagnosed originally as pneumonia (Fig. 186). Landsman[29] reported 3 such cases. Enlargement of the liver is almost always present, and without this the diagnosis should be made with caution. Slight to moderate leukocytosis and normal results of liver-function tests are of value in establishing the diagnosis. Since fecal examination may not disclose the presence of amebas, it cannot be relied upon to establish the diagnosis.

The diagnosis may be established firmly by roentgenographic and fluoroscopic observations. In early cases these changes may be mild, and only by careful examination are they detected. As the amebic hepatic infection progresses, however, the roentgenographic changes become obvious.

Demonstration of "chocolate-sauce" pus from material aspirated from the abscess usually establishes the diagnosis of amebic hepatic abscess. Exploratory aspiration probably should be performed whenever it is believed that the amebic process has reached the abscess stage. When the proper precautions are observed and the procedure properly performed, this method of diagnosis is entirely innocuous.

PROGNOSIS

The prognosis of hepatic amebiasis is dependent upon (1) the relative virulence of the organism and resistance of the host, (2) the stage of the infection, (3) the multiplicity of lesions in the liver, in the case of abscess, (4) presence or absence of secondary infection, and (5) the type of therapy employed.

The prognostic importance of the extent or the stage of infection is emphasized by the fact that in the series of De Bakey and Ochsner[17] the mortality rate was about 22 per cent for hepatic abscess, whereas for amebic hepatitis there were no fatalities. This striking difference emphasizes the importance of recognizing the earlier phases of amebic hepatic disease, a fact pointed out more than 30 years ago by Rogers,[45] who described it as the "presuppurative" stage.

In the presence of abscess formation, multiple abscesses may affect the prognosis seriously. This is particularly true when multiple abscesses are clinically demonstrable.

The presence of complications also has a grave influence on the prognosis of amebic hepatic infections. The development of pleuropulmonary involvement and of secondary infection of the hepatic abscesses radically changed the characteristics of amebic hepatic infection and increased the difficulty of treatment. Many differences exist between the relatively benign and limiting features of the purely amebic abscess and the rapidly invasive and septic type of pyogenic lesion of the liver. Thus the mortality rate for sterile abscesses is about 5 per cent, whereas that for abscesses secondarily infected is about 40 per cent.[17]

The type of therapy employed is also of prognostic import. It has been suggested that the use of antimicrobial agents, along with emetine or chloroquine closed drainage of amebic infections, may be employed despite the presence of secondary infection. However, our experience does not confirm these observations, and although antibiotic agents are of value in the presence of secondary infection in preventing systemic invasion and limiting extension of the process, in most instances adequate drainage will be necessary.

The superiority of conservative management with emetine and chloroquine, with or without aspiration, has been demonstrated clearly, and its prognostic importance is well documented.

When open drainage is necessary for complicated amebic hepatic abscesses, the prognosis is significantly better when drainage is accomplished without contamination of the pleural or the peritoneal cavity.

TREATMENT

In most instances of amebic hepatic infection conservative therapy is effective. During the stage of simple amebic hepatitis treatment consists in administration of one or both of the drugs which are specific for extra-intestinal amebiasis, namely, emetine and chloroquine. The amebacides commonly employed to control amebic infection of the intestinal tract are of little or no value in the treatment of amebic hepatic infection; therefore, it is extremely important that amebic hepatitis be recognized early in order that specific therapy in this presuppurative stage may be instituted.

For many years emetine hydrochloride has been the drug of choice in the therapy of extra-intestinal amebiasis. It is administered subcutaneously or intramuscularly in doses of 0.065 Gm. (1 gr.) daily until 0.39 to 0.65 Gm. (6 to 10 gr.) have been given. Emetine is essentially a protoplasmic poison with an apparent selective action on muscles. Thus, if the drug must be administered in excessive amounts or over a prolonged period of time, there is danger of toxicity, particularly from its effect on the cardiac musculature. For this reason, care should be exercised in its use. If a second course is indicated, an interval of 20 to 30 days should elapse before this is administered, to avoid cumulative toxic effects.[51] If the drug is administered in the dosage already outlined, clinical manifestations of toxicity are rarely encountered.

Chloroquine (7-chloro-4-[4 diethylamino 1-methyl butylamino] quinoline) is one o the nontoxic, highly active compounds o the 4 aminoquinoline series disclosed by the wartime antimalarial drug-research program. In the belief that its antiplasmodia activity might extend to other pathogenic protozoa and because of its high concentration in the liver (about 500 times its plasma concentration) and its almost complete absorption from the gastro-intestinal tract, it therapeutic effectiveness was investigated[10, 11, 12] in the treatment of 32 patients with intestinal amebiasis and 7 with hepatic amebiasis. The results, particularly in the treatment of patients with hepatic amebiasis were so striking as to lead others to emplo this agent in the treatment of amebic hepati abscess.[1, 19, 24, 31, 37, 48, 49, 54] Chloroquine i administered orally (chloroquine diphosphate) in a dosage of 1 Gm. daily for 2 t 3 days followed by 0.5 Gm. daily for 2 to weeks. No serious toxic manifestations hav been observed even after repeated course of therapy, although minor reactions such as headaches, pruritus, disturbances of visual accommodation, and gastro-intestina complaints are noted occasionally. Lik emetine, chloroquine is not always effectiv in the treatment of amebic hepatic disease

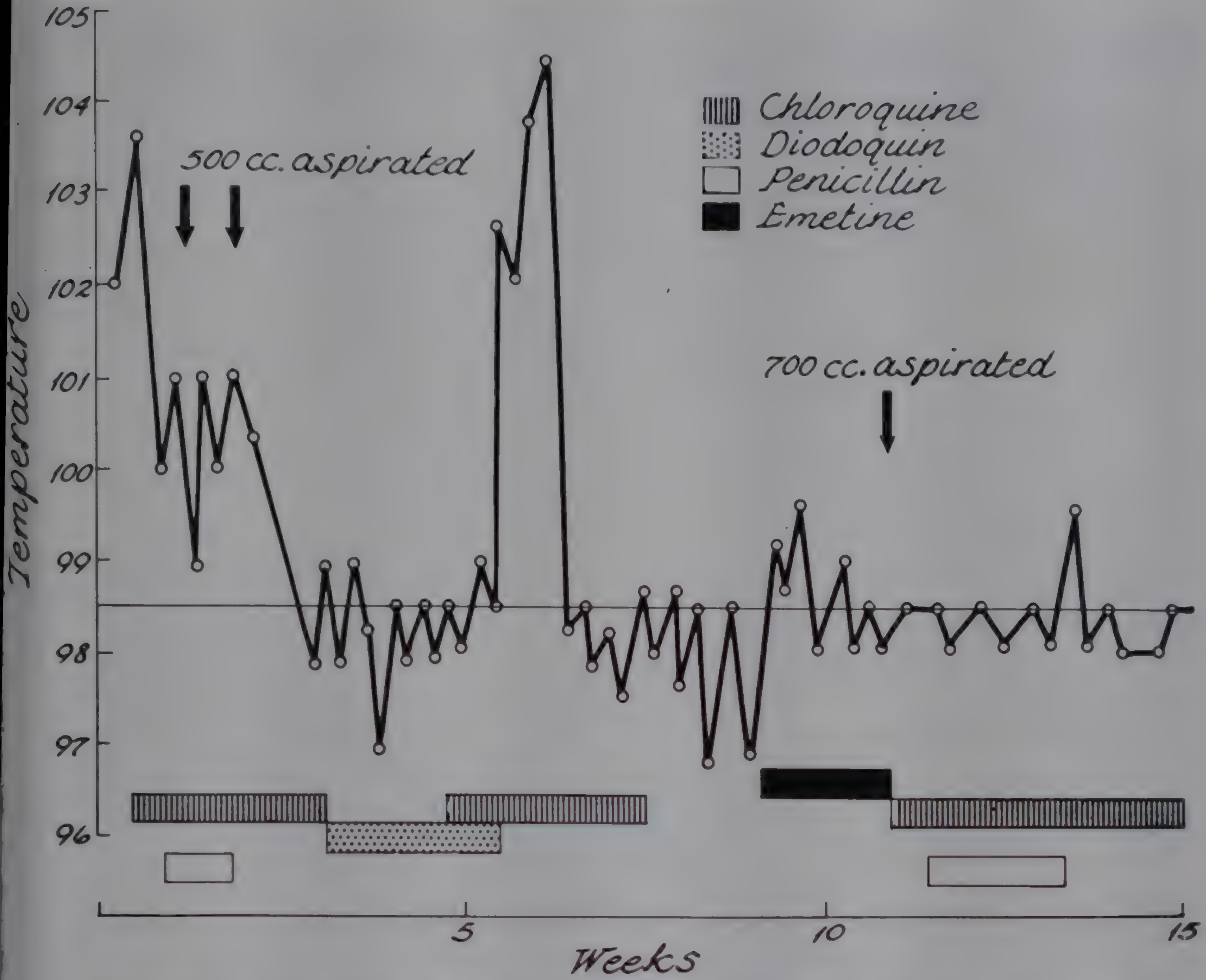


FIG. 185. Clinical chart of a patient with an amebic liver abscess. Chloroquine, Diodoquin, emetine and penicillin were administered, and aspiration was performed on 3 occasions, resulting in resolution of the abscess.

and failure to respond to chloroquine does not rule out this condition.[21] If either emetine or chloroquine alone fails to eradicate the amebic hepatic infection, dual therapy with these drugs may be effective.[50, 18]

Upon completion of therapy with emetine, or simultaneously during treatment with chloroquine, a full course of treatment with one of the intestinal amebacides should be administered. The iodochlorohydroxyquinolines, chiniofon and Diodoquin, have been employed extensively in the treatment of amebic colitis. Chiniofon is administered orally in dosage of 1 Gm. 3 times daily before meals for 7 to 8 days. Treatment with Diodoquin consists of administration of 2.5 Gm. of the drug daily in 3 or 4 divided doses for about 20 days. Recent studies indicate that Milibis (bismuth glycolylarsanilate) is also a valuable anti-amebic drug which is relatively insoluble and is absorbed rather slowly by the intestinal wall.[2, 3, 4, 25, 55] Hence, it is useful primarily in treatment of early acute amebic infections or in asymptomatic cases. Although it is reported to have a low toxicity, it should be prescribed with caution for patients who have an idiosyncracy to arsenic.[6, 50]

As mentioned previously, both emetine and chloroquine may be employed to advantage in the treatment of amebic hepatic abscess. Thus, emetine may be administered initially for 7 to 10 days followed by a course of therapy with chloroquine. During administration of chloroquine, one of the intestinal amebacides (chiniofon, Diodoquine, or Milibis) may be given (Fig. 185).

Although many antibiotic agents have

been employed in the treatment of amebiasis, the only 3 that appear to have any benefit are chlortetracycline (Aureomycin), oxytetracycline (Terramycin) and fumagillin.[37, 56] They have been employed primarily for the treatment of intestinal amebiasis. Tobie and associates[58] found that chlortetracycline and oxytetracycline have a high anti-amebic efficiency which lasts for about 2 weeks following a course of therapy. However, at 2½ months the number of ameba-free patients in the chlortetracycline-treated series had dropped to about 60 per cent, whereas in the oxytetracycline-treated group it remained high. Most and Van Assendelft[59] are of the opinion, based on 2 years' experience, that oxytetracycline is an effective amebacide. However, these antibiotic agents appear to have little or no effect on extra-intestinal amebiasis, and, in fact, development of amebic abscess of the liver during oxytetracycline therapy has been reported.

If clinical manifestations persist after administration of emetine or chloroquine, or if there is evidence of hepatic abscess, aspiration is indicated. Although the diagnosis of amebic hepatic abscess may be made at the outset, it is important to administer emetine or chloroquine for several days prior to aspiration.[16, 17] Aspiration always should be performed in the operating room under strict aseptic conditions to avoid contamination. Furthermore, open drainage may be done without delay in cases of secondary infection. Physical findings and roentgenographic studies will indicate the site of puncture. Local infiltration with a 1 per cent solution of procaine hydrochloride is preferable to general anesthesia. In the presence of localizing signs and pointing of the abscess, the aspirating needle may be inserted directly over the mass. It is important to avoid traversing the peritoneal or the pleural cavity. Thus, in the absence of localizing signs, the needle should be introduced through the tenth intercostal space in the anterior axillary line and directed upward, medially and backward. Should multiple aspirations become necessary, or if it is desirable to change the direction of the needle after it has been inserted, it should be removed entirely before it is reintroduced in order to avoid injury to the hepatic enchyma. As much of the liquefied ne material is removed as possible, and s and culture should be made immediate the smear contains numerous pyogeni ganisms, the abscess should be dr openly and promptly, care being take avoid contamination of the uninvolved ous cavity. It is not necessary to inje amebacide into the cavity following as tion. Repeated aspirations, when neces can be accomplished through the site for the initial aspiration.

Prior to aspiration, antibiotic th should be initiated. If the abscess is inf secondarily, the organism should be i fied promptly by culture, and antibiotic sitivity studies should be performed in to determine the most suitable agent.

Rarely, an amebic hepatic abscess not resolve completely following adr tration of emetine and chloroquine. multiple aspirations probably occur cause of the large size of the abscess and the extensive fibrosis in its wall, prevent closure of the cavity following age. Under these circumstances it ma come necessary to open the abscess w and close it by the use of a muscula from the abdominal or the thoracic w

COMPLICATIONS

Secondary infection with pyogenic isms, direct extension, or rupture of th scess into a serous cavity or an ad viscus are the most important complic of amebic hepatic infection. These a invariably occur in association with a formation and consequently are seen later stages of amebic hepatic disease. the importance of early recognition amebic hepatic infection is further e sized, for it is during this early presu tive stage that the process can be con with appropriate therapy and complic avoided.

Secondary Infection with Pyogeni ganisms. True amebic hepatic abscess bacteriologically sterile and when py organisms are demonstrable, they are ably secondary invaders. Under the cumstances, a change occurs both nature of the abscess contents and

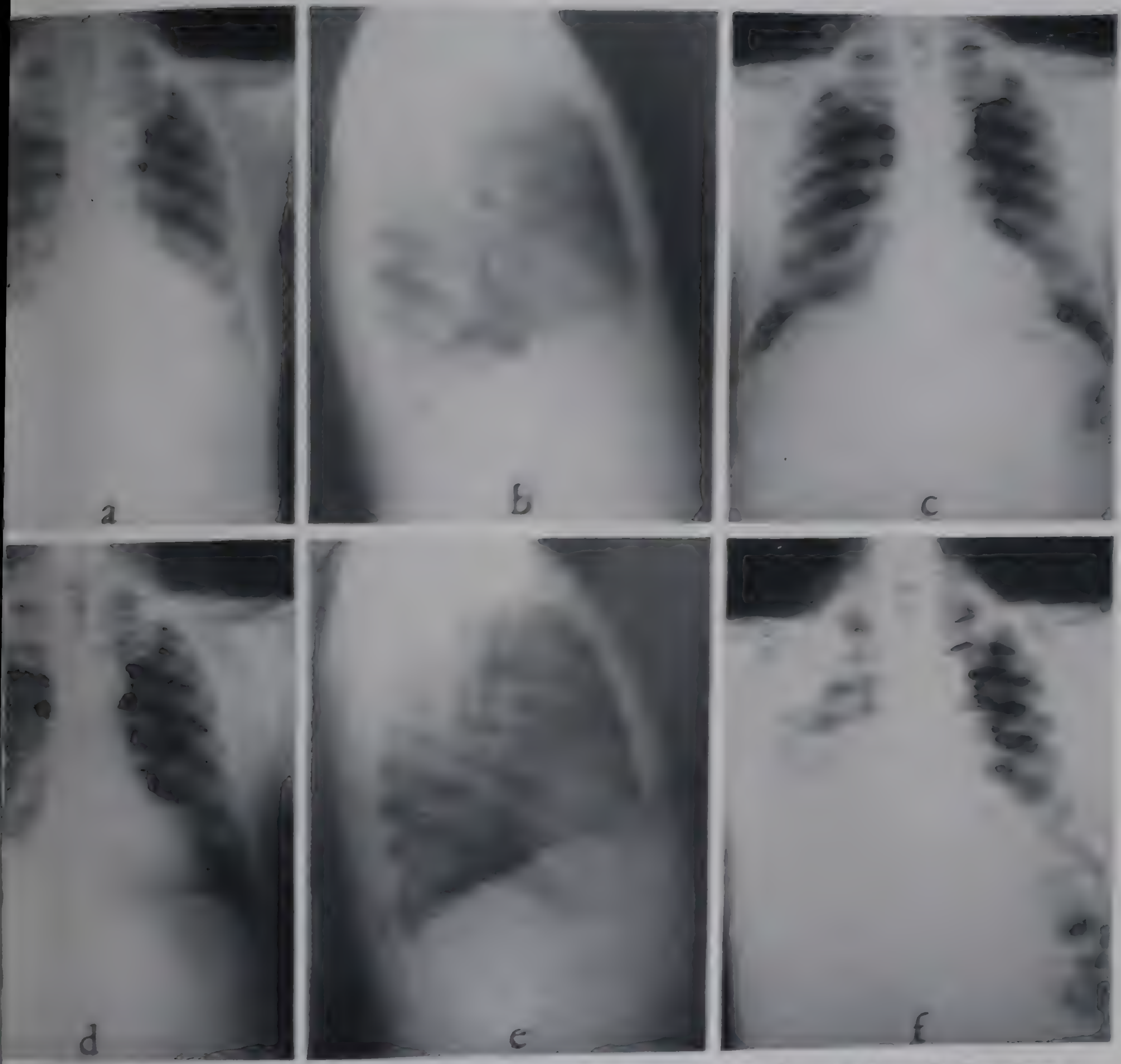


Fig. 186. Serial chest roentgenograms taken during a 7-month period and showing
gradual development of an amebic hepatic abscess. (a) Anteroposterior view taken
January, 1952, because patient complained of pain in the right lower chest. There is
ght elevation of the diaphragm and blunting of the cardiophrenic angle. The roentgeno-
am was reported to show "pneumonitis." (b) The lateral projection, taken at the same
ne as (a), discloses elevation of the anterior portion of the diaphragm and obliteration
the anterior costophrenic sulcus. (c) Anteroposterior roentgenogram taken in March,
52, because of persistence of symptoms. There is irregularity of the right diaphragm
d blunting of the cardiophrenic angle. (d and e) In July, 1952, anteroposterior and
eral roentgenograms disclose progression of the diaphragmatic changes. There is now
dence of pulmonary parenchymal changes at the right base. (f) Anteroposterior
ojection taken about 2 weeks after roentgenograms shown in (d) and (e). The right
g field is now obscured by a pleural effusion. The patient developed a bronchohepatic
tula, and after treatment with emetine and chloroquine, and thoracentesis, he recovered.

manifestations. The typical "choco-
auce" pus becomes purulent, may
a greenish-yellow or grayish-yellow
ance and frequently is malodorous.
linical manifestations become more severe with a higher, usually spiking, fever and leukocytosis. Most commonly, streptococci and staphylococci are found in the purulent material removed from the abscess, although pneumococci, enterococci and

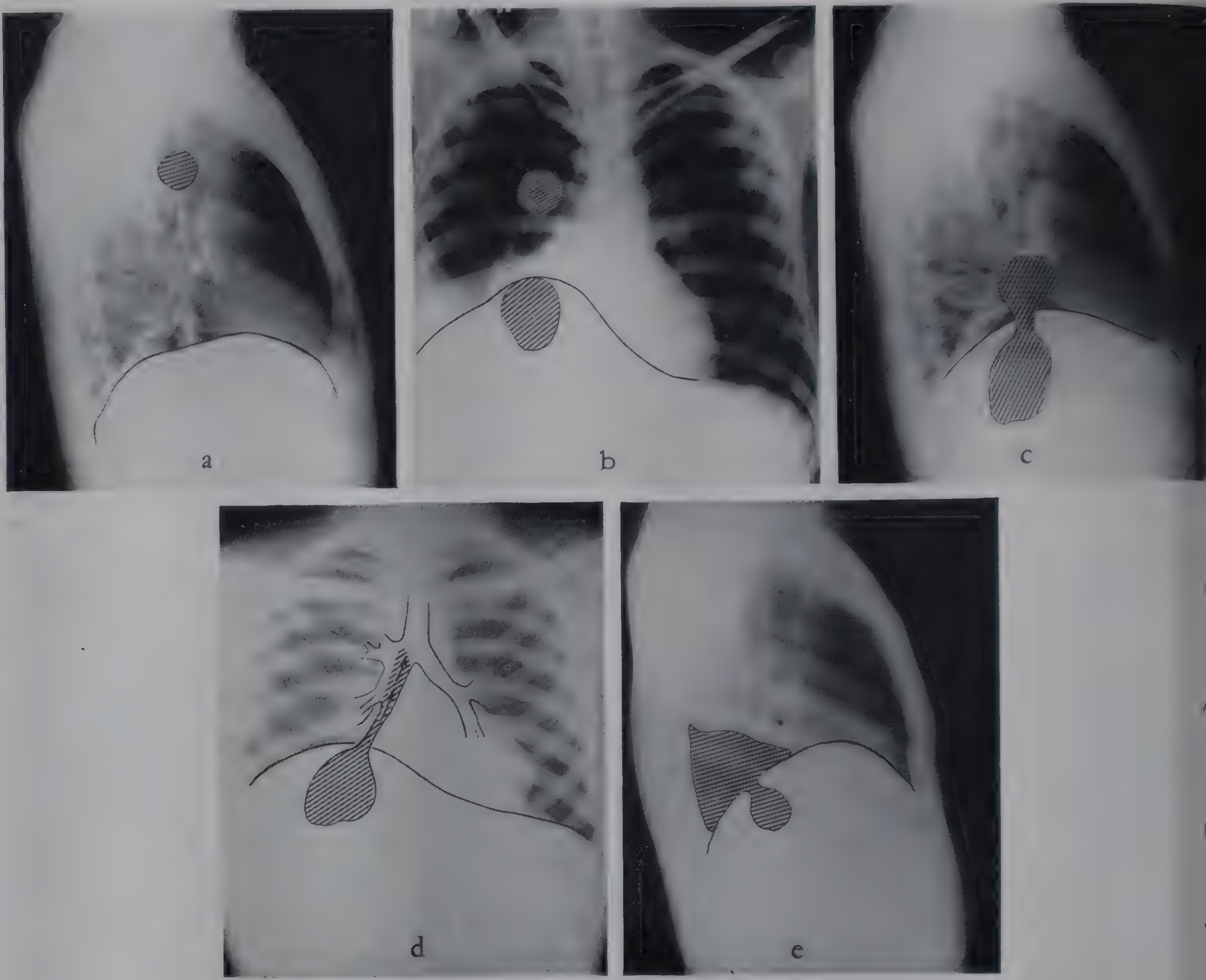


FIG. 187. Retouched roentgenograms demonstrating the types of pleuropulmonary complications of amebiasis. (a) Pulmonary abscess without hepatic involvement. (b) Independent pulmonary and hepatic abscesses. (c) Pulmonary abscess extending from hepatic abscess. (d) Bronchohepatic fistula. (e) Empyema extending from a hepatic abscess.

colon bacilli may be observed also. The incidence of secondary infection ranges between 10 and 20 per cent.[17, 30] Secondary infection may have a significant effect on the prognosis, as might be expected. Thus, in a series reported by De Bakey and Ochsner,[17] the mortality was 46.1 per cent among patients with secondary infection and only 11.1 per cent among those where no secondary infection was present. Although vigorous antimicrobial therapy should be employed in the treatment of patients with a secondarily infected amebic hepatic abscess, in most instances this will not obviate the necessity for adequate prompt open drainage.

Pleuropulmonary Involvement. The nex most frequent complication is pleuropulmonary involvement. Usually, this represent rupture or direct extension of the hepati abscess through the diaphragm, althoug rarely it may be due to systemic invasion. Pleuropulmonary amebic infections may b divided into 5 types, according to their gros pathologic characteristics: (1) hematogenous pulmonary abscess without hepati involvement (Fig. 187a), (2) hematogenou pulmonary abscess and independent hepati abscess (Fig. 187b), (3) pulmonary absces extending from hepatic abscess (Fig. 187c) (4) bronchohepatic fistula (Fig. 187d), an (5) empyema extending from a hepatic a

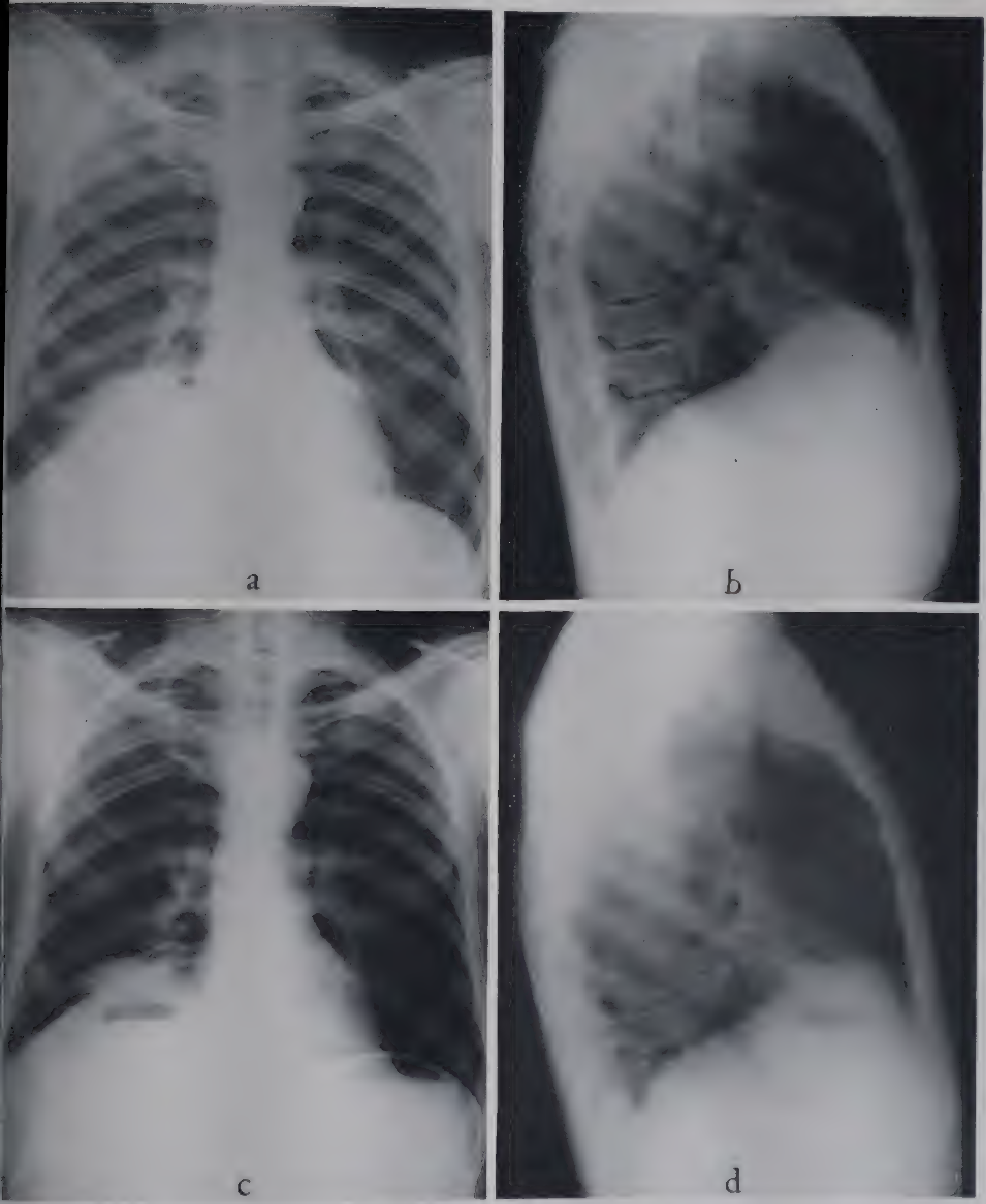


FIG. 188. Roentgenograms of patient with a pulmonary abscess extending from an amebic hepatic abscess. (a) Postero-anterior projection, showing elevation of the right leaf of the diaphragm and blunting of the cardiophrenic angle. A small abscess cavity is visible within the density at the right lung base. (b) Lateral projection reveals an abscess cavity above and immediately below the diaphragm. (c and d) Anteroposterior and lateral roentgenograms taken after aspiration of the hepatic abscess and institution of emetine and chloroquine therapy.

scess (Fig. 187e). The last 3 are by far the most common.

Although there is convincing evidence that pleuropulmonary amebiasis may result from systemic invasion by the ameba, most commonly it is the result of direct extension from an amebic hepatic abscess and usually follows perforation through the diaphragm or occasionally transphrenic migration by way of the lymphatics. Occurrence of this complication is dependent particularly upon virulence of the infection, resistance of the host, and location of the process in the liver. Most amebic hepatic abscesses are located near the convex surface and in the posterior portion of the right lobe of the liver, and the adjacent diaphragm is invaded readily and incorporated by the abscess as it enlarges, thus permitting extension into the thoracic cavity (Fig. 188). The abscess may rupture into the base of the right lung or into the free pleural cavity, depending upon the severity of the process. A more rapidly progressing abscess largely associated with a pleural reaction of sufficient degree will produce obliterative adhesions so that the abscess usually will rupture into the pleural cavity. Following rupture into the pulmonary parenchyma a bronchial fistula may result which permits evacuation of the contents of the abscess through the tracheobronchial tree (Fig. 189). This latter event usually occurs in abscesses which develop slowly and in which the pleural cavity has been obliterated by adhesions.

Pleuropulmonary complications occur only in patients with true amebic hepatic abscess, the incidence being about 15 to 20 per cent.[17] About 40 per cent of these complications are primarily pleural with empyema, the remainder being primarily pulmonary. The latter are divided about equally between bronchohepatic fistulas and pulmonary abscesses communicating with the hepatic abscess.

Characteristically, pleuropulmonary complications are associated with pain in the right lower region of the chest, frequently extending to the right shoulder, unproductive cough, and slight or moderate dyspnea, in addition to the usual manifestations of amebic hepatic abscess, which become more pronounced as the abscess encroaches upon the chest. In some instances these symptoms suddenly become more prominent, and the patient begins to cough up large quantities of purulent "chocolate sauce" material. This establishes the presence of a bronchohepatic fistula.

Physical examination discloses characteristic signs of consolidation or cavitation, particularly in the right lower pulmonary area. The diagnosis is confirmed by roentgenographic examination. Fluoroscopy may demonstrate elevation and immobilization of the diaphragm. Roentgenograms usually reveal increased density in the lower right pulmonary field, and in both the anteroposterior and the lateral views a triangular shadow may be seen extending upward from the liver toward the hilum of the lung. If the abscess ruptures into the pleural cavity, the roentgenographic picture is one of pleural effusion or empyema. Introduction of iodized oil into the trachea will visualize accurately a bronchohepatic fistula.

Treatment of pleuropulmonary complications is determined by the type of involvement and the presence or the absence of secondary infection. Emetine or chloroquine should be given to all patients. In the presence of a bronchohepatic fistula, conservative therapy, consisting of administration of emetine or chloroquine and postural drainage, is usually adequate. In some instances bronchoscopy may be helpful in evacuation of the abscess. If, after the development of bronchohepatic fistula, the hepatic abscess is still prominent, aspiration should be performed. In the absence of secondary infection conservative therapy, consisting of aspiration of the hepatic abscess and the pleural effusion, also should be employed. The value of more definitive surgical therapy in certain forms of pleuropulmonary complications of amebic hepatic abscess has been emphasized recently by Shaw.[46] He believed that in the presence of empyema that does not respond to repeated aspiration, persistent bronchohepatic fistula, or chronic pulmonary abscess, the most effective therapy is thoracotomy with removal of the products of infection, including decortication of the lung and the diaphragm and resection of the involved portion of the lung.

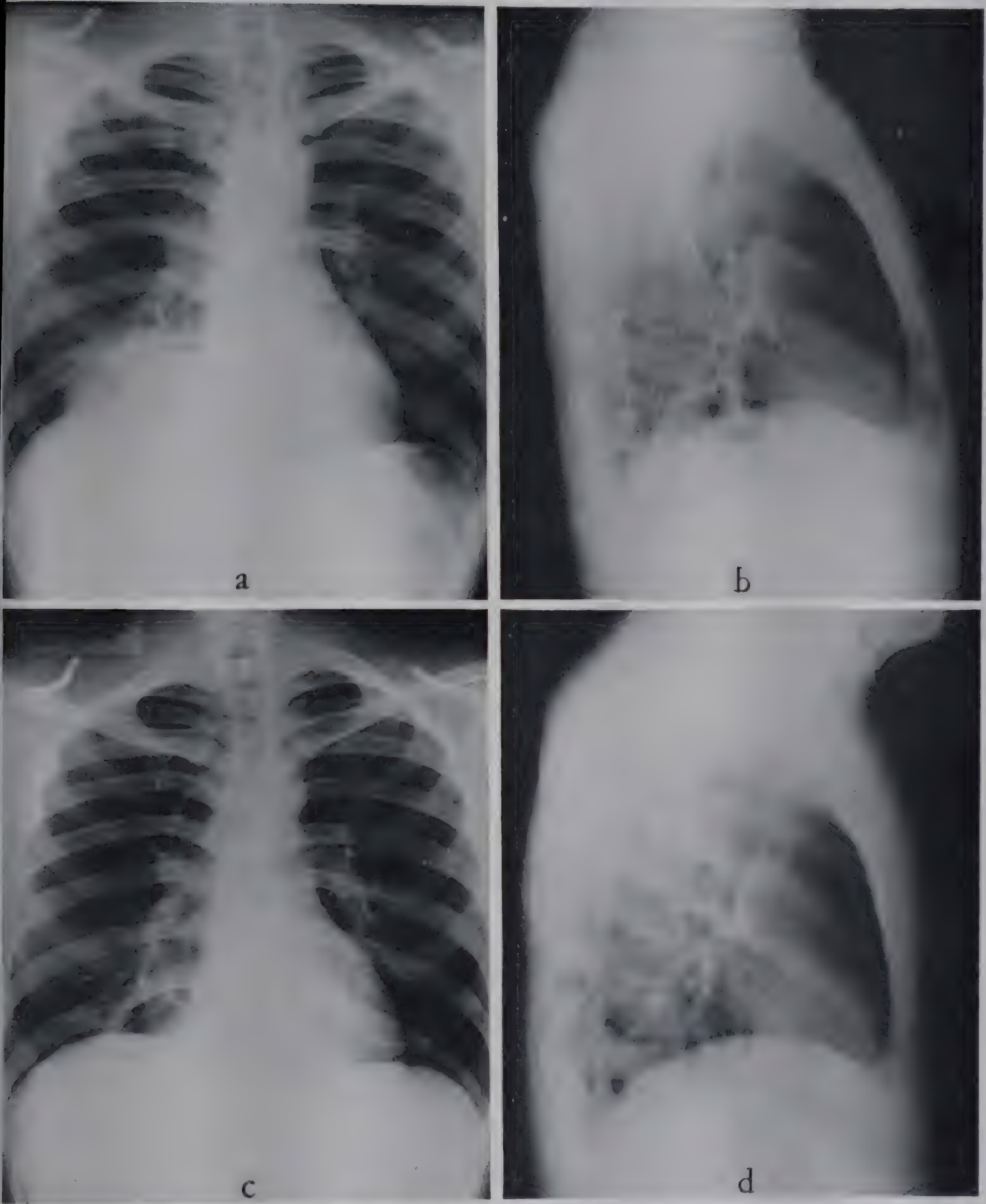


FIG. 189. Roentgenograms of patient with an amebic hepatic abscess complicated by a bronchohepatic fistula. (a) Anteroposterior projection, showing elevation of the right leaf of the diaphragm and obliteration of the right cardiophrenic angle. (b) Lateral view shows the elevation to involve primarily the anterior portion of the diaphragm. The anterior costophrenic sulcus is obliterated. (c and d) Anteroposterior and lateral roentgenograms taken after development of a bronchohepatic fistula. The hepatic abscess cavity is outlined by the air-fluid level. A triangular shadow extends from the diaphragm toward the pulmonary hilum and represents the course of the bronchohepatic fistula.

Rupture of Amebic Hepatic Abscess. 1. INTO PERITONEAL CAVITY. Rupture of an amebic hepatic abscess into the peritoneal cavity is the next most frequent complication, occurring in from 6 to 9 per cent of patients with true abscess.[17] The seriousness of this complication is indicated by the mortality rate of about 75 per cent. However, the prognosis in general depends upon whether there is localized or generalized peritonitis with extension of the abscess into the peritoneal cavity. If the abscess progresses gradually, there is stimulation of peritoneal adhesions along the inferior surface of the liver so that the process becomes walled off with the formation of localized peritonitis. If, on the other hand, rapid extension occurs, and particularly if the abscess is infected secondarily, perforation and rupture into the virgin peritoneal cavity will produce generalized peritonitis. This type of complication is much more severe than the former type. In the treatment of the patients emetine or chloroquine always should be administered, and in the majority of cases open drainage is necessary because of the presence of secondary infection.

2. INTO PERICARDIAL CAVITY. Rupture of an amebic hepatic abscess into the pericardial cavity has been reported by several observers.[17] It usually occurs with an abscess of the left lobe of the liver and is characterized clinically by sudden manifestations of pyopericardium and collapse. In some instances associated pericarditis rather than pericardial abscess has been reported. Most reported cases of true perforation have terminated fatally.

3. OTHER AREAS. Other unusual complications of amebic hepatic abscess include rupture of the abscess into the gastrointestinal tract, into the biliary tract, into the portal vein and the inferior vena cava, through the abdominal wall, and extension to the spleen and the kidneys. Cerebral abscess has been reported,[17, 32] but often it is preceded by hepatic and pleuropulmonary involvement. Halpert and Ashley,[22] who reviewed the literature on this subject in 1944, found that only 5 cases, including their own, of the 61 reported up to that time were not associated with either hepatic or pulmonary involvement. Since then, at least 6 cases have been reported, of which all but 2 were associated with hepatic or pleuropulmonary involvement. All reported cases have terminated fatally, with the possible exception of a recent case of Collard and Kendall[9] in which the diagnosis of cerebral amebiasis was based essentially on the "dramatic response to emetine." These complications represent far advanced and often neglected stages of the disease, and the small number of such instances reported in the recent literature is perhaps indicative of the awareness of amebic hepatic infection and the institution of prompt therapy in the early stages.

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Chapter 23

LIVER DISEASES IN INFANCY AND CHILDHOOD

Wolf W. Zuelzer, M.D.

INTRODUCTION

In early life the liver differs significantly from the adult organ in structure, function and response to local and systemic influences. Though designed ultimately to assume a central role in metabolism, it is still predominantly an organ of hemopoiesis as late as the middle part of fetal life. Its erythropoietic activity does not cease entirely until birth and is still marked in premature infants at that time. Under pathologic conditions the infantile liver continues or readily resumes its hemopoietic function. At birth the circulatory conditions in the liver are modified to some extent by the closure of the ductus venosus, but, more importantly, the largely untried organ is subjected to the newly arising demands of extra-uterine life. The ability of the liver to meet these demands is a variable justly regarded as a measure of functional maturity.[13] This factor, though difficult to measure, is important since it determines to a large extent the effect of physiologic and pathologic challenges. Many of the disturbances likely to affect the liver in the neonatal period are thus characteristic of the age group and rarely if ever occur in later life. Conversely, the common diseases of the adult liver are rare in infancy. Familiarity with the peculiarities of early infancy is therefore essential for a successful approach to the problems which the infantile liver presents to the clinic and to the laboratory.

DEVELOPMENT AND STRUCTURE

The liver develops as an outgrowth of the entodermal tube in the region of the future duodenum. The primary branching of the hepatic diverticulum furnishes the liver anlage proper, the gallbladder and the cy duct. Disturbances of development in region are not uncommon and produce varied patterns of atresia of the extrahep bile ducts. The liver anlage proper is for by branching cell cords which invade splanchnic mesoderm and differentiate pr imally into the hepatic ducts and distally secretory hepatic tubules. The intertubu spaces are filled by sinusoidal vessels aris from the breakup of the omphalomesent veins as they pass through this region. radial growth of secretory tubules from branches of the hepatic ducts produces secretory lobules the center of which formed by the bile ducts accompanied branches of the portal vein and the hep artery. The overlapping radial system growth of the hepatic veins simultaneo produces the vascular lobules of the which are visualized more readily and more familiar to the student of histol These structures are centered around hepatic veins from which a radiating pat of polygonal cells extends toward the po tracts.[36] The development of the hepatic cords from the hepatic ducts in the center the secretory lobules according to this cla theory makes it difficult to accept the o sional reports of isolated atresias of the trahepatic bile ducts in the presence of mal lobular patterns in the liver.[1] Failur development of these ducts should lea agenesis of the secretory lobules norm arising from them. Moreover, such a pro would require that one accept the assu tion of identical defects arising simult ously in millions of separate units of hepatic anlage.

At birth, in the full-term infant the tral veins and the portal triads are well fined, but the radial pattern of the cell is less distinct, and the lobular boundaries are less well-defined than in the adult liver. In the premature infant and under pathologic circumstances in the full-term baby as well, the presence of more or less extensive hemopoietic foci further tends to obscure the architecture. These foci are composed of erythrocyte precursors developing within the cell cords and also found scattered in the lumens of the sinusoids. Their presence correlates well with nucleated red cells circulating in the peripheral blood. Hepatic hemopoiesis is frequently marked in erythroblastosis fetalis, in which condition it appears to represent a compensatory phenomenon in the presence of hemolysis. For less-well-known reasons it also occurs in infants born to diabetic mothers[32] and in many infections, notably congenital syphilis. Granulocyte precursors also may be found under these conditions but are limited to the connective tissue about the portal triads.

The gross shape of the liver at birth is essentially that of the adult organ, but the two lobes are still more nearly equal in size than those of the adult liver. Occasionally, right and left lobes may show striking differences in appearance due to greater or lesser congestion, fat content or even hemorrhage or necrosis in one lobe than in the other. These differences have been shown to be related to the drainage of the two lobes by separate branches of the hepatic veins.[20]

The capsule is thin and easily lifted or even ruptured by hematomas collecting underneath as the result of mechanical trauma sustained during birth. The weight of the liver is greater in proportion to total body weight than that of the adult liver but highly variable, as is, of course, the birth weight itself. The figure given by Coppoletta and Wolbach[7] for the weight of the organ at birth, 78 Gm., is probably too low; that given by Potter and Adair,[39] 150 Gm., is on the high side. It is clear that only very large deviations can be regarded as significant, and it must be kept in mind that the enormous dilatation of the sinusoids of the liver seen especially in asphyxiated infants may rapidly increase the weight of the organ. Even in healthy infants the liver is normally palpable at birth and remains so to a greater or lesser degree for about 2 years, a fact which tends to make the clinical appraisal of hepatomegaly hazardous at times.

THE LIVER AND JAUNDICE IN THE NEWBORN PERIOD

The central fact in any consideration of the neonatal liver is the occurrence of icterus as a physiologic phenomenon. Although recent evidence regarding the effect of blood group incompatibilities between mother and child has narrowed down the definition of physiologic icterus, the concept remains valid and is essential for the understanding of all types of jaundice in the newborn period.

The classic studies of Davidson, Merritt and Weech[13] established the fact that the bilirubin level is elevated in the cord blood of most newborn infants. After birth the curve of the serum bilirubin rises rapidly, reaching a peak about the third or the fourth day and declining somewhat more gradually thereafter. The higher the initial level in the cord blood the higher is the peak likely to be attained. The elevation of the total bilirubin is due almost entirely to an increase in the indirect fraction. The degree of bilirubinemia observed in seemingly normal infants varies considerably, and it is still somewhat hazardous to set an arbitrary upper limit on what may be regarded as physiologic. It is clear that the values obtained at any given moment must be interpreted in terms of the time elapsed since birth, and that a bilirubin level which might well be physiologic for an infant 3 or 4 days old might be grossly abnormal in an infant less than 24 hours old. In a recent study by Hsia et al.[27] the cord blood values ranged from 1.4 to 3.2 mg. per cent; those obtained at 3 to 4 days, from 0.6 to 13.2 mg. per cent. In the author's laboratory 3 mg. for cord blood and 10 mg. at 3 to 4 days are regarded as approximate physiologic maxima in full-term infants.[56] Premature babies generally tend to show more severe and more prolonged icterus than do full-term infants.

Although hyperbilirubinemia is a universal phenomenon in the newborn period, clinical jaundice is not. Depending somewhat on conditions of observation, icterus is observed in from one third to two thirds of newborn infants. When the concentration of bilirubin in the serum exceeds 4 to 5 mg. per cent the vast majority of infants show frank icterus. Below this level the presence of clinical jaundice is highly variable and seems to depend largely on capillary permeability and other factors connected with the circulatory system and the state of the skin and other tissues. The time of onset of physiologic icterus is variable, but it is becoming increasingly evident that jaundice in the first 24 hours is not to be regarded as normal but always as an indicator of a disturbance, however mild.

The commonest cause of such early jaundice in otherwise seemingly normal infants appears to be the mild hemolytic anemia sometimes resulting from incompatibility of the major blood groups A, B and O between mother and child. In a recent study[57] of all instances of icterus in the first 24 hours after birth which could not be accounted for otherwise, nearly all infants were found to belong to blood group A or B and their mothers to blood group O. The significance of ABO hemolytic disease and of "icterus praecox," the term coined by Halbrecht[22] for the mild, otherwise asymptomatic form of this condition, was not known when the basic studies on physiologic icterus were undertaken. Davidson and his associates, whose material included 25 per cent of infants found to be icteric on the first day of life, did not take the blood groups of the patients and their mothers into consideration; therefore, their data are subject to revision. It is firmly established, however, that physiologic icterus occurs in entirely normal infants whose blood groups are compatible with those of the mothers.

The time when physiologic jaundice should subside and the bilirubin levels should approach those of the adult is likewise difficult to determine. In most infants the jaundice has disappeared by the end of the first week. Any increase in the severity of icterus after the first week is likely to have pathologic significance. The persistence of jaundice of any degree after the third week of life is almost certain to be abnormal.

The prevailing views concerning the nature of physiologic icterus have gone through several phases in which alternately inadequacy of hepatic function and accelerated hemolysis have been regarded as primarily responsible for the accumulation of bilirubin The pendulum has not yet come to rest completely, but there is now substantial agreement on the importance of the hepatic element in physiologic jaundice. To be sure, the type of bilirubin which is increased in this condition is associated ordinarily with hemolysis. Rapid destruction of fetal erythrocytes in the newborn period as part of the adjustment to a more abundant oxygen supply has been postulated again and again as the basic mechanism in neonatal jaundice. Conclusive proof of such a process is still lacking. The main obstacle to a solution of this problem lies in the difficulties of measuring accurately the blood volume and the red cell mass of the newborn as the basis for assessing the extent of neonatal hemolysis. However, even when allowance is made for an increased rate of hemolysis, this process would seem to be minor in degree and certainly, as Mollison[33] has shown, incapable of accounting for the jaundice if hepatic function were entirely adequate.

Direct proof of the functional inferiority of the newborn liver has been slow in forthcoming. Many of the standard liver function tests indicate an adequate performance by the neonatal liver. However, Yudkin[54] and his associates and others[34] have demonstrated that the excretion of bromsulphalein is impaired in the majority of newborn infants. The excretion of bilirubin has also been shown to be less efficient in the first few days of life than later on.[47] Moreover, a significant relationship has been established between the clearance of bilirubin by the neonatal liver and the degree of bilirubinemia observed in a given infant.[15] In addition there is indirect evidence of considerable weight to incriminate the functional state o the liver as the essential factor in neonata icterus. The elevation of the bilirubin leve of the cord blood cannot be explained in terms of postnatal hemolysis. Barring an accelerated breakdown of red corpuscles in the antenatal period, this phenomenon indicates inefficient excretion of bile pigment even in utero. While the relative importance of the liver and the placenta in the elimination of bilirubin from the fetal blood stream not known, it is likely that the major load alls on the placenta. Very little bile is found n meconium. The fact that infants born with ongenital atresia of the biliary tract do not s a rule show intense jaundice at birth also ndicates that in utero the liver plays a relaively minor part in the excretion of bile. It s likely that placental excretion becomes indequate some time before birth and before he liver is adjusted to the load now imposed pon it. The relationship between the initial ilirubin of the cord blood and the subseuent peak level has been mentioned and rovides further evidence for the importance f the equilibrium between load and capacity f the liver at the moment of birth.

The inadequacy of hepatic function with espect to bilirubin excretion is an individual ariable which is expressed customarily as nmaturity of the neonatal liver. This conept is in accord with the greater and more rolonged bilirubinemia observed in premaure infants. However, it is conceivable that ther factors besides the development of epatic function might influence the initial ilirubin level—for example, variables in lacental circulation, intra-uterine oxygen upply or the mechanics of intra-uterine ressures.

In the present state of our knowledge it eems fair to describe the situation as folows: At birth and for a short time thereafter he excretory "reserve power" of the liver for ilirubin is much closer to the actual demand han at any other time, so close in fact that ven slight increases in the load may exceed he capacity of the organ and result in reention bilirubinemia. The truth of this reaoning—and the determining role of the liver n this equilibrium—is borne out time and gain in a situation in which there is frank athologic hemolysis, namely, in erythrolastosis fetalis. The degree of jaundice freuently bears no direct relationship to the everity of the hemolytic process in this disase. With apparently minimal hemolysis ome infants exhibit extreme bilirubinemia. onversely, pronounced hemolysis may be ssociated with minimal icterus, evidently ecause the liver is functioning adequately. he physiologic variability of neonatal heatic function is magnified, as it were, by the nposition of an unphysiologic demand. Since hyperbilirubinemia in itself appears to be a major hazard in this period, the newborn liver by virtue of its physiologic properties thus comes to occupy a central position in the pathophysiology of hemolytic diseases of the newborn.

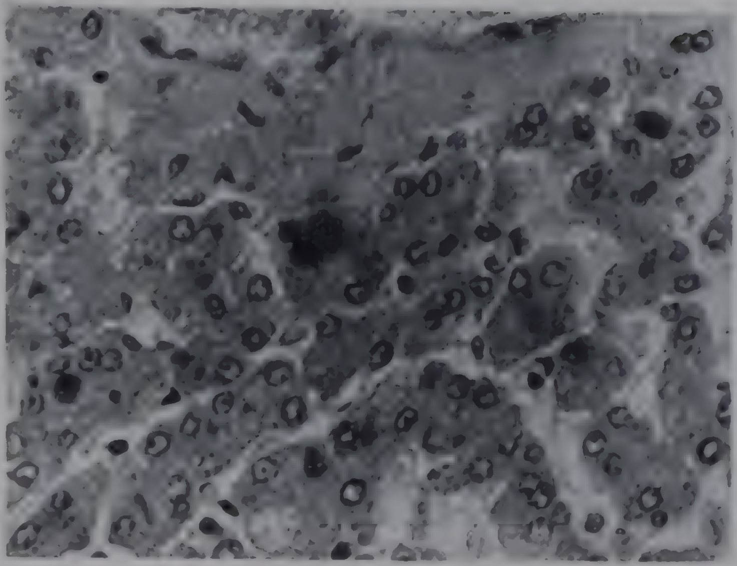


FIG. 190. Plugs of inspissated bile. From 8-day-old infant dying after unsuccessful operation for congenital atresia of jejunum. No icterus. Liver otherwise normal.

The foregoing remarks imply that there is no sharp border between physiologic and pathologic icterus in the newborn period. Now it must be added that the distinction hemolytic and "obstructive," or retention and regurgitation, jaundice also is made less easily at this time than in later life. In the presence of a high level of indirect bilirubin, whatever the cause of its accumulation may be, the liver of the newborn infant and particularly of the premature very frequently exhibits so-called bile "thrombi," apparently inspissated plugs of bile which fill and distend the intercellular bile canaliculi. From its location, appearance and staining reactions this material may be assumed to be actual bile which has been excreted in such concentrated form that it becomes inspissated, thereby causing obstruction to the further free flow of bile into the larger ducts. This event seems to take place in the absence of obstruction at the level of extrahepatic bile ducts and in the absence of clinical or histologic evidence of structural liver disease. It creates a vicious circle in that the excreting capacity of the liver, already taxed by the original demand, must now become further impaired. The precise mechanism which leads to the inspissation of bile in an apparently organically sound liver is not known. Apart from severe bilirubinemia itself, it would appear that dehydration such as may occur with relative ease in the newborn is a common contributory factory. The event itself is a fairly common one, judging from the frequency with which inspissated bile is found in closely studied autopsy material. Recently, Hsia and his associates[29] have called attention to the "inspissated bile syndrome" which is reversible and must be distinguished from true organic obstruction and from parenchymal liver disease. However, cases with clinical manifestations of obstructive jaundice represent only a minority of the instances in which inspissation of bile is found histologically. In the majority of neonatal livers containing bile thrombi studied histologically by the author the inspissation was either insufficient in degree or too short in duration to produce the classic clinical picture of biliary obstruction. Apart from erythroblastosis with severe jaundice, the chief conditions in which inspissated bile thrombi are found are prematurity, diarrhea, vomiting, intestinal obstruction and severe sepsis.

DIFFERENTIAL DIAGNOSIS OF JAUNDICE IN THE NEWBORN PERIOD

After what has been said about the behavior of the newborn liver under physiologic and pathologic conditions it is not surprising that in this age jaundice is more often the expression of some systemic disorder affecting the excretory function of the liver than it is an indication of primary disease in the biliary tract or liver itself. Even when the liver is involved structurally, the process is more often than not part of a generalized illness, as for example in congenital syphilis and in certain viral infections characteristic of the age group.

PHYSIOLOGIC ICTERUS

This condition is characterized by lack of signs and symptoms, by delayed onset, transient character and absence of abnormal findings in blood and urine. Though the older texts generally state that deeply jaundiced infants with physiologic icterus ma show some lethargy, and though even suc symptoms as vomiting and thermal instabi ity have been attributed to physiologic jaun dice it is at least questionable whether suc a state should still be called physiologi even if the basic mechanisms are the sam When such pathologic manifestations d occur it is certainly a safer attitude to con sider the infant as potentially ill and to b prepared to investigate the condition and t initiate proper therapy.

Of the time-honored triad of commo causes of pathologic jaundice in the new born, syphilis, sepsis and erythroblastos fetalis, only the last-named condition re mains numerically significant. Erythroblasto sis fetalis, or hemolytic disease of the new born, is in fact the commonest cause o neonatal icterus, especially if the definitio includes cases due to incompatibility of th major blood groups of mother and child a well as the Rh system.

HEMOLYTIC DISEASE DUE TO RH ANTIBODIES

The clinical picture is more variable tha was realized before the advent of reliab serologic diagnosis. The usual picture is th of icterus developing within a few hou after birth and progressing rapidly. Som degree of anemia is present in most case although it does not necessarily parallel th degree of jaundice and in fact may be a sent for some days in infants with partic larly profound icterus. However, the bloo picture in the average case does clearly r flect the presence of a hemolytic process wi reticulocytosis, polychromasia and norm blastemia beyond the degree found in no mal infants. Liver and spleen, as a rule, a more or less enlarged. Occasionally, p techial bleeding is noted. The diagnosis res on the demonstration of incompatibility b tween mother and child in the Rh system, o the presence of maternal antibody effecti against the infant's red corpuscles and on th demonstration of a positive direct antiglo ulin test in the infant's blood. The bilirub in the cord blood is often elevated beyon the physiologic range. In the next few hou and days it rises rapidly, sometimes to a most unparalleled levels. While nearly all he bilirubin is usually of the indirect variety, here are cases in which, almost from the eginning, the direct-reacting fraction is also levated, though to a lesser degree, rarely ccounting for more than a quarter of the otal. Prior to the widespread use of exhange transfusion with Rh-negative blood delayed rise in the direct reacting bilirubin vas not uncommon, and sometimes such nfants developed the clinical and laboratory icture of obstructive jaundice with bile apearing in the urine, and stools becoming cholic, while the skin assumed a greenish inge instead of the earlier orange-yellow. ersistence of jaundice for 4 to 6 weeks in uch cases was not uncommon. With the se of exchange transfusion with Rh-negaive blood the jaundice tends to disappear nuch more rapidly, often dramatically vithin a few days, as if the excretory funcions of the liver were suddenly becoming dequate.

The histologic picture of the liver in rythroblastosis varies somewhat with the tage of the disease. Hemosiderosis of modrate degree is usually found. In addition, he parenchymal cells may show swelling nd granularity of the cytoplasm and, in ases of severe icterus, bile thrombi and ytoplasmic granules of bile and necrosis of olygonal cells may be found. Hematopoitic foci may be abundant and create the mpression of displacement or replacement f polygonal cells. The involvement of the iver rarely leads to residues such as fibrosis r cirrhosis. The older literature contains lescriptions of such instances[24] but the diagiosis of erythroblastosis fetalis at that time ested on uncertain grounds and recently ew such reports have appeared.[8]

A complication of jaundice peculiar to the eonatal period and common in erythroblasosis, though not specific for this condiion,[2, 58] is the occurrence of neurologic nanifestations connected with yellow staing of certain areas of the brain and usually poken of as kernicterus. In this condition he clinical picture varies from mild spasticty and lethargy to loss of the Moro reflex, pisthotonus and frequently death. In surivors, atelectasis, spastic paralysis and nental retardation may be observed. Infants lying with kernicterus in the newborn period show more or less extensive bright yellow discolorations of certain cerebral nuclei, notably the thalamus, the hypothalamic nuclei, the cornu ammonis of the hippocampus, the flocculi and the dentate nucleus of the cerebellum and the nuclei in the floor of the fourth ventricle.

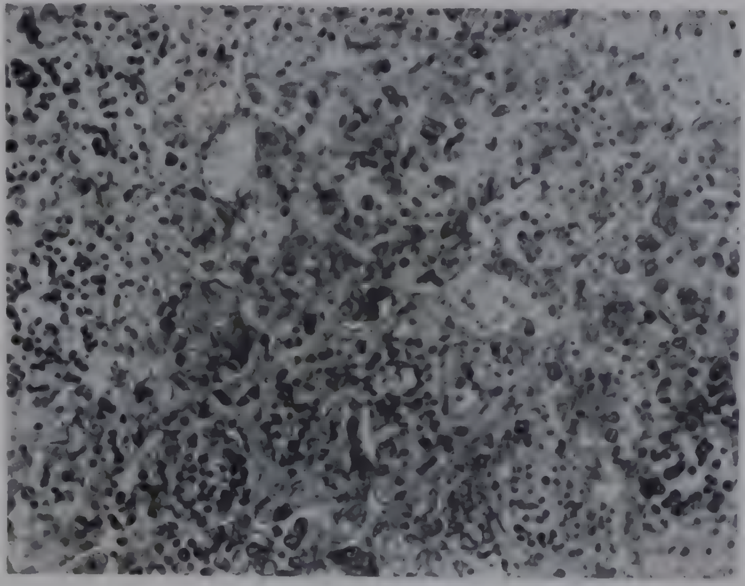


FIG. 191. Necrosis and dissociation of polygonal cells, congestion, extensive hemopoiesis. Liver of 15-hour-old infant dead of hydropic-anemic form of erythroblastosis fetalis. This is an example of unusually severe liver damage in this disease.

Histologically, one finds varying degrees of necrosis and necrobiosis of ganglion cells in the affected areas. The pathogenesis of kernicterus is still uncertain. It is not yet clear whether the lesions are due to the action of bilirubin itself reaching the brain tissue in high concentration through a permeable blood-brain barrier in the newborn, whether a special toxic type of bilirubin is involved or whether the bilirubin merely stains already damaged tissue. Thus far kernicterus never has been observed in jaundice due to biliary atresia but it has been found in newborns with conditions other than hemolytic disease, notably in prematures. A fairly good correlation has been shown to exist between the intensity of the bilirubinemia[28] and the likelihood of kernicterus. If the views expressed above are correct to the effect that bilirubinemia in the newborn is chiefly the result of inadequate hepatic function, it would appear that the development of kernicterus is a main hazard of hepatic immaturity. In cases in which kernicterus results from hemolytic disease, exchange transfusion has proved to be an effective preventive measure, the rationale being the replacement of red corpuscles about to be destroyed, by blood not susceptible to the effect of the maternal antibodies.[35] The prevention of kernicterus in instances not attributable to hemolytic disease remains an unsolved problem.

ABO HEMOLYTIC DISEASE

Evidence for the existence of a clinical syndrome in the newborn infant due to maternal antibodies against the blood group factors A or B has been accumulating during the last decade. Today there is virtually unanimous agreement on the occurrence of such a condition, although the criteria for its diagnosis are not as yet well established. The chief and often the sole clinical feature is icterus, usually beginning within 24 hours after birth and progressing in most instances for 3 to 4 days, at which time the bilirubin level may exceed 30 mg. In about 10 to 15 per cent of the untreated cases kernicterus develops.[57] However, in most cases the jaundice is mild and tends to disappear far more rapidly than in Rh hemolytic disease. The mildness of the clinical manifestations is in fact such an outstanding feature of most cases that frequently the condition is overlooked. For the same reason Halbrecht[22] who was among the first to draw attention to the condition, termed it icterus praecox.

As a rule, the liver is only slightly enlarged. The spleen is not palpable in the majority of cases. Anemia is not always present and is rarely severe, but reticulocytosis is nearly always found and indicates the occurrence of a more-or-less compensated hemolytic process. A characteristic feature of the blood is a transient spherocytosis.[21] The osmotic fragility of the erythrocytes is increased accordingly.[10] The serologic diagnosis of ABO hemolytic disease presents certain difficulties. No one test has been satisfactory thus far. The direct Coombs test with the infant's erythrocytes is usually negative or at best very weakly positive, at least with standard commercial antiglobulin sera available in this country. The combination of blood groups, mother O, infant A or B while prerequisite to the diagnosis, is not nearly as suggestive as is the combination mother Rh-negative, infant Rh-positive in Rh hemolytic disease. Approximately 20 to 25 per cent of all pregnancies are heterospecific in the sense that the maternal serum contains agglutinins active against the fetal blood group; yet obviously most heterospecific pregnancies do not affect the infant. The height of the maternal anti-A or anti-B agglutinin titer is not reliable. Marked increases in titer are suggestive, but frequently the titers as measured in saline are within normal range. Attempts have been made to characterize so-called "immune" anti-A and anti-B antibodies in the maternal serum as opposed to the natural α and β agglutinins. Hemolysis of A or B cells by such sera,[11] the presence of an antibody not neutralized by A or B soluble substance[50] and elevation of titers in certain hydrophilic media[49] have been found to be properties of "immune" sera. However, thus far none of the tests have given consistent results in cases with the clinical features of ABO hemolytic disease, while conversely such immune sera may be found in women whose offspring prove to be entirely normal. In the author's laboratory a battery of tests is employed. The most consistent results have been obtained with the indirect Coombs test performed with the infant's serum and homologous cells (A or B), using group O cells as controls.[57] The presence of free antibody effective against cells of the infant's own blood group is strong presumptive evidence for ABO erythroblastosis, especially in the presence of otherwise unexplained early icterus.

The main threat to the infant with ABO hemolytic disease appears to lie in the development of kernicterus. In a series of cases of sufficient severity to lead to a clinical diagnosis of ABO hemolytic disease studied in this laboratory, 10 per cent of the infants developed kernicterus. The use of exchange transfusions with group O blood in a manner similar to that with Rh-negative blood in Rh hemolytic disease appears to prevent this complication but would seem to be indicated only in severely icteric and premature infants.

Familial Nonhemolytic Jaundice in the Newborn

This interesting condition was described recently by Crigler and Najjar[12] in 7 infants related through a common ancestor. The salient features are the development of early severe icterus which persisted and was associated with the neurologic manifestation of kernicterus in 6 of the 7 cases. There is marked elevation of the indirect fraction of the serum bilirubin and retention of bilirubin on excretion tests, but the other liver-function tests are normal, and histologic examination of the liver shows only inspissation of bile in the canaliculi. The prognosis is poor, most of the patients dying in the first year of life. The authors regard the condition as a genetically determined abnormality in excretory hepatic function.

Atresia of the Bile Ducts

Only the clinical and diagnostic aspects will be considered here. Infants with atresia of the bile ducts often show little or no jaundice at birth and for some time may appear to be normal in every respect. Sooner or later, however, jaundice becomes apparent and persists from that time on, showing only an ncrease in intensity or remaining stationary but never decreasing. The skin eventually assumes a greenish hue. The meconium is not unusual, but the subsequent stools are white or clay-colored. As the concentration of bile pigments in the body increases, the secretions such as tears and the juices secreted into the gastro-intestinal tract become bile-stained, and in this manner some small amounts of bile may reach the stools. The urine contains bile at all times. The liver gradually increases in size. Much later, arely before several months of age, the pleen becomes enlarged. For long periods of time the general state of health and nurition of the patients with unrelieved biliary obstruction is surprisingly good, but eventully the infants become malnourished and pecifically develop rickets. At one time this form of rickets was regarded as a specific ype, "hepatic" rickets, but now it is agreed that the development of rickets in these inants is due simply to the inadequate absorption of fat-soluble vitamin D in the absence of bile from the intestinal tract.

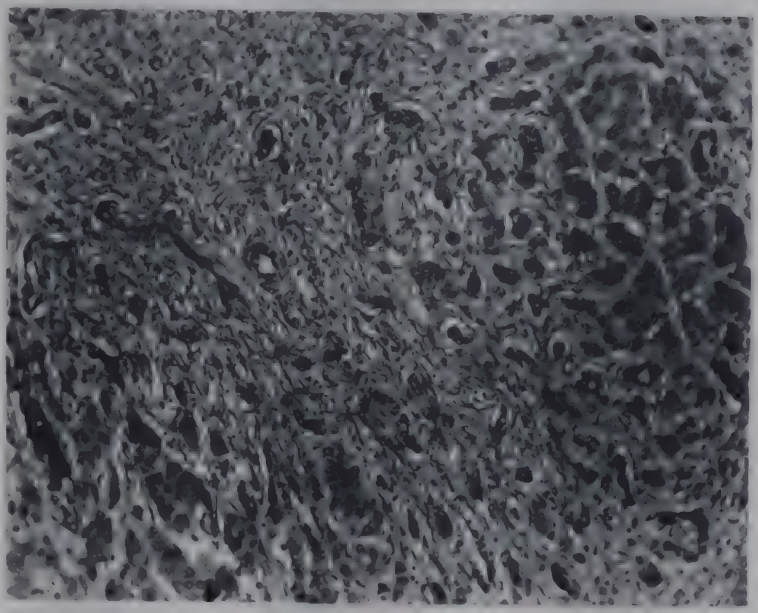


FIG. 192. Obstructive biliary cirrhosis secondary to congenital atresia of hepatic duct in a 2-year-old child.

The laboratory findings, at least in the early stages of the condition, are not remarkable except for the marked elevation of the serum bilirubin which is of the direct reacting variety. The liver-function tests fail to show any disturbance. Unfortunately, this negative finding is not as helpful in the differential diagnosis in early life as it is later on. Even in proved infectious hepatitis of young infants the tests, such as cephalin flocculation and thymol turbidity, frequently have been found to be normal. The diagnosis of biliary atresia is not an emergency and can be postponed safely until prolonged observation of the unvarying obstruction and increasing icterus justify surgical exploration.

The "inspissated bile syndrome" is most likely to be confused with biliary atresia. The distinction is important because exploratory surgery is indicated only in the latter condition. If the jaundice is intermittent, atresia is less likely than obstruction by secretions. However, the persistence of obstruction over long periods of time may simulate organic occlusion of the biliary passages. The use of cholagogues, such as magnesium sulfate and decholin, has been advocated[37] to stimulate the flow of bile. If after several weeks of trial there has been no evidence of a flow of bile as judged by examination of the duodenal contents or of decreasing icterus, laparotomy is definitely indicated. If surgical repair is not feasible, biliary cirrhosis develops, ascites and hypoprothrombinemia may occur, and the patient eventually dies of malnutrition, hepatic failure, or intercurrent infections. Survival up to 3 and 4 years has been recorded, but of course all patients die unless the obstruction can be relieved by surgical means.

SEPSIS

Neonatal sepsis is no longer the major problem it once was but it still must be considered among the conditions associated with icterus. As used in current pediatric practice, the term denotes a variable symptom-complex rather than either a demonstrable bacteremia or any etiologic or pathologic entity. It implies the spread of micro-organisms from a portal of entry or primary focus by way of the blood stream and the likelihood of metastatic suppuration. It is not always possible to demonstrate anatomic lesions, nor can bacteremia be shown to exist in every case. Moreover, organisms not ordinarily considered as pathogenic, particularly members of the *E. coli* group, may be obtained in blood cultures; and unless such bacteria prove to be present on several occasions it may be impossible to decide whether they are contaminants or play a significant role in the patient's illness. The portal of entry may be the umbilicus, but there are many other possible sites, such as skin abrasions, mucous membranes, respiratory tract and genitalia. Often it is impossible to demonstrate the portal of entry by the time the clinical manifestations of a systemic illness have appeared. The clinical picture is variable, depending among other things on the localization of single or multiple metastatic lesions which may involve many organs or systems. Fever is not always present; in fact, the temperature is often subnormal or merely unstable. Leukocytosis is not a constant finding. Anemia is likely to develop rapidly. The infant with sepsis appears toxic and lethargic, nurses poorly, often vomits and may have a hemorrhagic tendency. Jaundice often is among the first symptoms, and both liver and spleen may be enlarged. Icterus attributable to sepsis rarely makes its appearance before the third or fourth day of life. Sepsis is particularly likely if jaundice develops toward the end of the first week or becomes more marked in an infant whose initial physiologic icterus has begun to subside.

The mechanisms responsible for the development of jaundice in association with sepsis may vary and are not always clear. If the onset is early, at first the icterus may be physiologic and merely continue in an infant whose illness is bound to aggravate and prolong the functional immaturity of the neonatal liver. In certain infections hemolysis undoubtedly contributes to the excretory burden of the liver. In either case it is chiefly the indirect reacting bilirubin which accumulates in the serum. As in physiologic icterus and in hemolytic disease of the newborn, inspissation of bile may complicate the picture and lead to a rise of the direct-reacting bilirubin and to bilirubinuria. In most instances of neonatal sepsis the liver, although enlarged, shows no histologic changes indicating structural impairment except perhaps for inspissation of bile and mild degenerative changes in the polygonal cells. On the other hand, some infections ascending from the umbilicus may give rise to suppurative hepatitis and extensive destruction of hepatic tissue.

Sepsis not infrequently develops as a complication of some other neonatal illness, such as hemolytic disease of the newborn. Ordinarily, the diagnosis of sepsis rests on the general clinical picture, the demonstration of localized infections such as meningitis, osteomyelitis and the like, a positive blood culture and last, but not least, the exclusion of maternal isoimmunization and other causes of neonatal icterus.

CONGENITAL SYPHILIS

Congenital syphilis was at one time a major cause of severe jaundice in the newborn. Today, in this country at least, it has almost ceased to be a problem, largely as the result of better prenatal care and of the newer antiluetic agents. The disease varies in its effects on the liver. In severe cases the liver is literally riddled with spirochetes and shows a picture of so-called miliary gummata, actually acute foci of necrosis, and inflammation, usually in association with a diffuse intralobular fibrosis and cirrhosis. A the other extreme are cases in which the

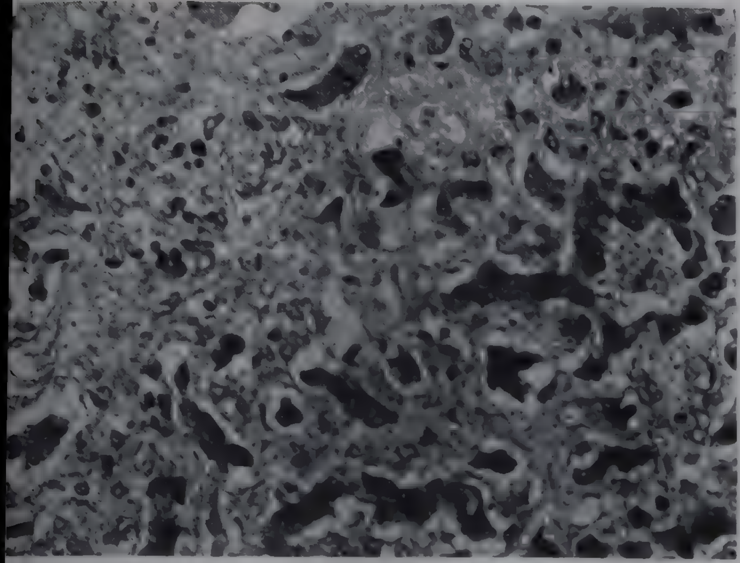


FIG. 193. Congenital syphilis, diffuse hepatic fibrosis and focal inflammatory changes. A 1-month-old infant, admitted with coryza, bleeding, desquamation of skin, hepatosplenomegaly and anemia. Kahn test positive. Innumerable spirochetes were found in liver and other tissues.

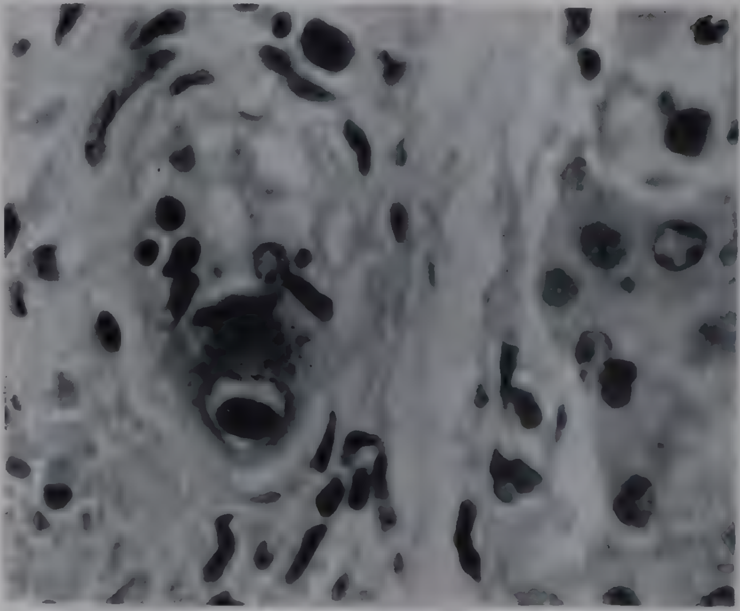


FIG. 194. Typical intranuclear and cytoplasmic inclusions in epithelial cell of small intrahepatic bile duct of 1-month-old icteric infant who had shown purpura, anemia, hepatosplenomegaly, terminal bleeding and cyanosis.

ver undergoes no structural change and at
nost may contain small numbers of spiro-
hetes. Severe involvement of the liver in
ongenital syphilis usually is accompanied by
terus, hepatosplenomegaly, anemia, and
ften spontaneous hemorrhages. The diag-
osis is made on the basis of clinical evi-
ence such as coryza, cutaneous and mucous
sions, osteochondritis and periostitis with
heir characteristic radiologic appearance
nd, of course, positive serologic tests. In
very unexplained case of icterus in the new-
orn period syphilis should be excluded by
suitable serologic method.

VIRAL INFECTIONS

Apart from infectious hepatitis which is
ow known to occur in earliest infancy but
ill be discussed separately, the liver of the
ewborn infant is peculiarly susceptible to
iral infections which do not seem to cause
epatitis in older individuals. To be sure,
e infections in question, herpes simplex
nd the virus of cytomegalic inclusion dis-
ase, involve many other organs and cause
mptoms not specifically related to the liver.
requently, however, hepatitis due to one of
ese agents is the main source of symptoms,
d the liver is the organ showing the greatest
involvement or the greatest amount of damage.

Cytomegalic Inclusion Disease. Although the virus responsible for this condition has not been transmitted to animals, it is virtually certain that it is a virus that causes the striking and characteristic cytologic changes which gave the disease its name. In guinea pigs and other rodents the development of almost identical lesions had been proved to be due to a virus which can be passaged but appears to have species specificity.[53] In man, the typical inclusions are found with especial frequency in the salivary gland, and originally the condition was referred to as salivary gland inclusion disease and was thought to be an incidental finding without clinical significance. More recently, it has been realized that there may be widespread involvement of many organs, including the liver, that the virus induces degenerative changes and necrosis and that it may cause symptoms and death of the organism as a whole.[43, 53]

The affected cells are commonly enlarged; they contain large single acidophilic intranuclear inclusions and basophilic granular inclusions in the cytoplasm.[6] Varying degrees of inflammatory response and necrosis may be evident. The virus appears to localize in epithelial structures in many parts of the

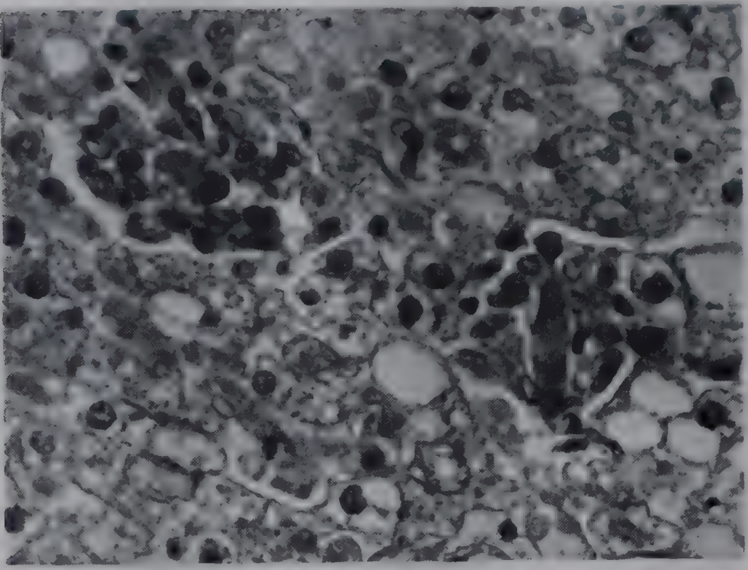


FIG. 195. Focal necrosis of inclusion-bearing cells surrounded by granuloma-like inflammatory reaction. Liver of 7-month-old infant with hepatomegaly, diarrhea and acidosis.

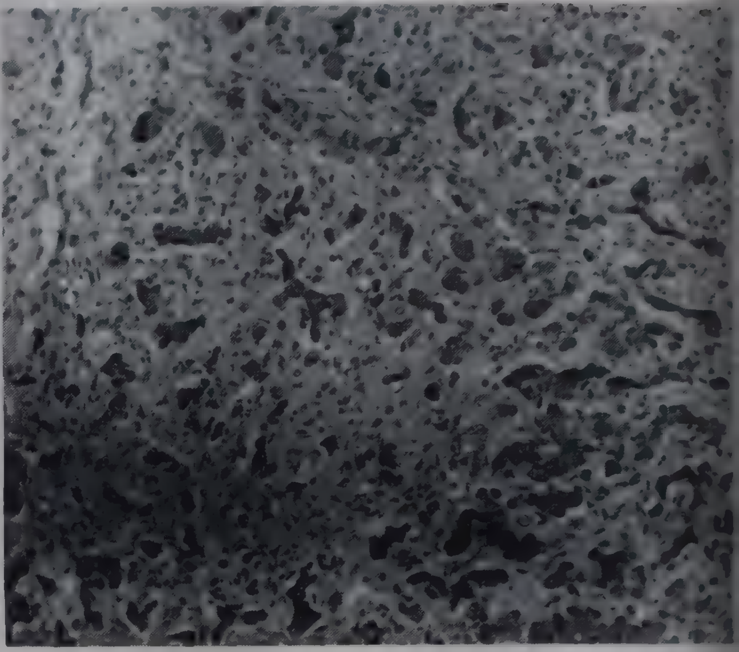


FIG. 196. Advanced stage of cytomegalic inclusion disease. Diffuse fibrosis of liver. Note similarity to picture in congenital syphilis (see Fig. 193). From 2-month-old infant with icterus, microcephalus, hepatosplenomegaly, diarrhea and dehydration. Innumerable cytomegalic inclusions in kidneys, pancreas, intestine, but rare in liver. Serologic tests and stains for spirochetes were negative.

body. In addition to the salivary glands, often the kidneys are involved, and characteristic changes have been observed in the liver, the pancreas, the lungs, the adrenals, the thyroid, the parathyroid, the gastro-intestinal tract and the brain. The writer has observed the typical picture in the pituitary in one case. With such a wide and variable distribution it is not surprising that the clinical picture is extremely protean, depending on the severity and the localization of the infection. The condition has been found with considerable frequency in stillborn infants, indicating the transplacental transmission of the virus which usually seems to produce no symptoms in the mother or in adults generally. In the newborn the disease may give rise to a clinical picture resembling hemolytic disease due to blood-group incompatibility with jaundice, anemia and normoblastemia. Thrombopenia and purpura have been found consistently in infants dying from the disease during the newborn period. The liver, as well as the spleen, are enlarged. From the beginning, the direct-reacting bilirubin is increased, and bile is present in the urine. The histologic picture of the liver is that of a hepatitis with cellular necrosis, hemorrhage and periportal fibrosis. The characteristic inclusions are found in the epithelium of the bile ducts and less easily in the polygonal cells. In infants surviving the newborn period or developing signs of the disease at a later age, hepatitis due to the virus of cytomegalic inclusion disease does not often dominate the clinical picture but has been reported by several authors The symptoms are those of diarrhea, abnormal bleeding tendency, deepening jaundic and sometimes ascites. The later stage i characterized by a diffuse intralobular fibrosis which often bears considerable resemblance to the picture of congenital syphilis The distinction is all the more difficul because by this time inclusions may be ver difficult to find, at least in the liver itself. Th laboratory findings in proved cases have no permitted the differentiation of this conditio from other acute hepatitis. In 2 cases observed by the writer in which the patien recovered and the diagnosis remained tentative, the liver-function tests remained abnormal, and the enlargement of liver an spleen persisted for many months. Interes ingly, both patients exhibited a strong col agglutinin in their serum which the matern serum failed to show. The diagnosis may b suspected in the newborn period[53] in the fac f the combination of purpura, and hepatitis with features of hemolytic disease when lood-group incompatibilities and congenital yphilis can be ruled out. Ordinarily, the iagnosis has been made only postmortem on istologic examination. In one instance the demonstration of inclusion-bearing cells in he urinary sediment led to a clinical diagnosis[16] of cytomegalic disease. As yet no pecial form of therapy has been devised.

Hepatitis Due to Herpes Simplex Virus. For many years the virus of herpes simplex vas considered as capable only of causing elatively trivial infections of the epithelial urfaces of skin and mucous membranes. In 935 Hass[23] described inclusions indistinguishable from those caused by the herpes virus in the liver and the adrenals of a premature infant. In 1952 Quilligan and Wilson,[40] and independently Zuelzer and Stulberg,[59] isolated herpes simplex virus from he livers of newborn infants. The latter uthors described 5 cases and since then they have observed 2 additional cases of herpes simplex hepatitis in newborn infants in which he virus was isolated. The nature of the condition was recognized by the typical intranuclear inclusions. Though the disease is generalized with evidence of the presence of virus in many organs and tissues, the involvement of the liver is particularly marked and argely seems to determine the clinical picure. The disease has been observed chiefly n premature infants. The virus may enter hrough the skin, the umbilicus and the mucous membranes when infective material, usually from the mother or a nurse, is present. The lesion at the portal of entry may be hidden or inconspicuous, and the disease does not become apparent until the virus has propagated extensively in the liver and other rgans. The liver enlarges rapidly, the infant ecomes lethargic, there is rapidly deepening cterus, cyanosis, dyspnea, bleeding from various sites and severe hypoprothrombinemia. At autopsy the liver appears to be tudded with white or yellow nodules which rove on histologic examination to be areas f coagulation necrosis. The intervening arenchyma is not normal, however, but hows degenerative changes, disruption of ell cords, beginning necrosis and hemorhage. In several of the cases described over

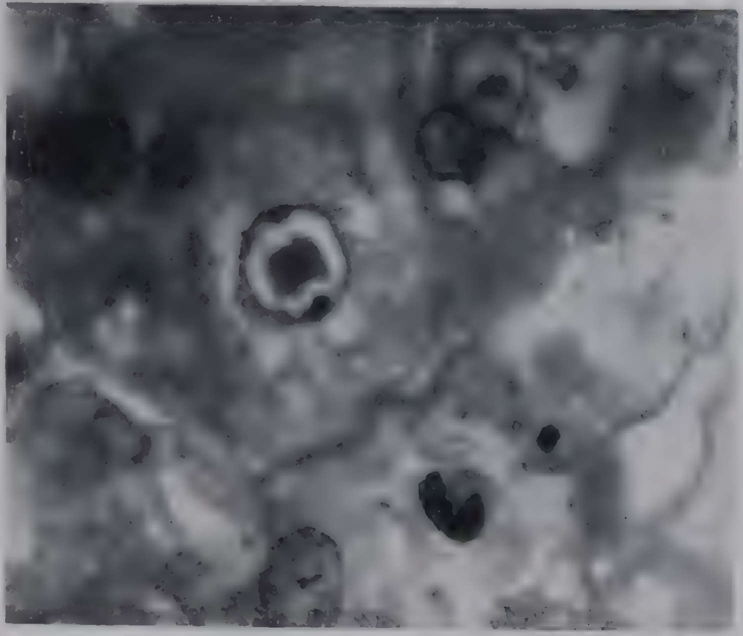


Fig. 197. Typical herpetic inclusion body and ballooning of cytoplasm of polygonal cell in liver.

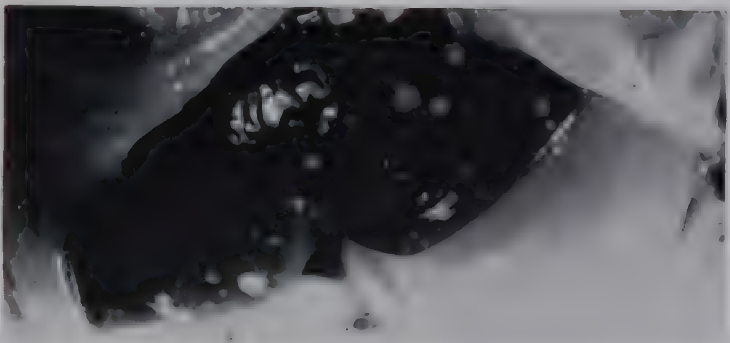


Fig. 198. Gross appearance of herpetic hepatitis. Multiple umbilicated whitish nodules in hemorrhagic liver. A 12-day-old premature infant with clinical picture of "sepsis." Icterus, bleeding, hemorrhages.

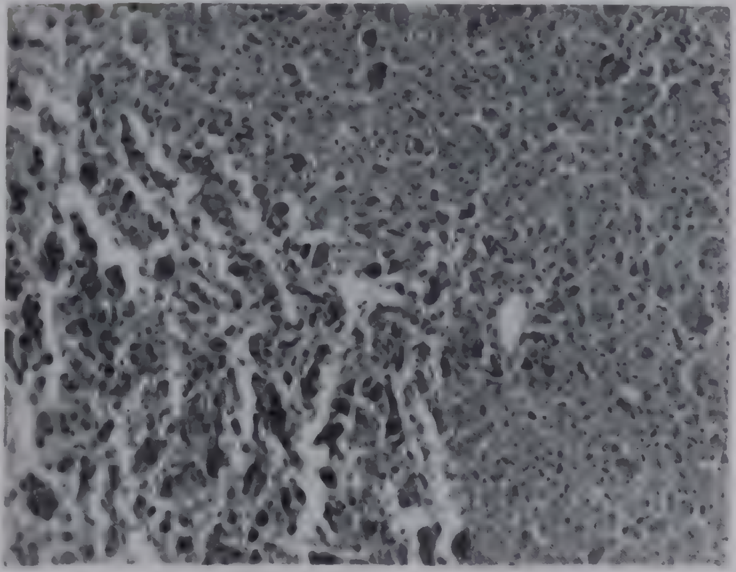


Fig. 199. Border zone between completely necrotic and partially preserved parenchyma in herpetic hepatitis.

75 per cent of the hepatic parenchyma was found to be completely destroyed.

The diagnosis thus far has been made only postmortem. The development of a sepsislike picture in an infant after the first 5 to 6 days of life should arouse the suspicion of herpetic hepatitis and of viremia, especially if exposure to an adult with active herpes can be established. If vesicles are found on skin or mucous membranes, their contents should be studied. If no bacteria are found, the probability of viral lesions, i.e., herpes simplex, becomes very great. As yet therapy is experimental. Gamma globulin or a hyperimmune antiherpes serum may be employed along with supportive measures such as transfusions.

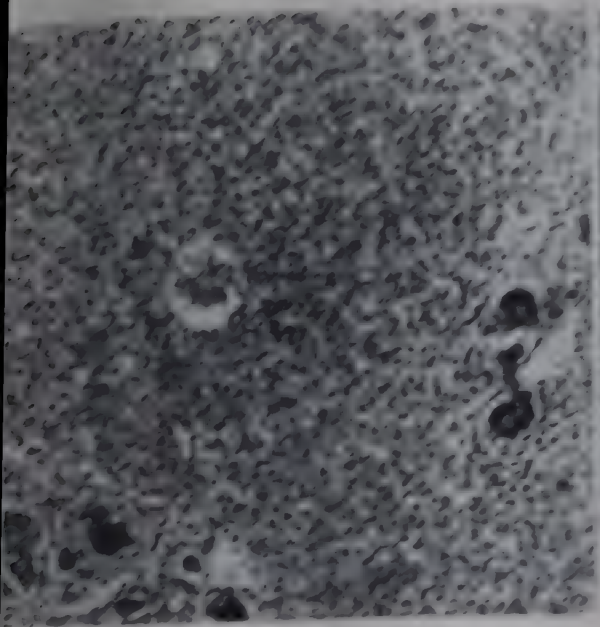
In older infants with herpetic stomatitis a focal hepatitis with herpes inclusions has been found in several patients who died.[59] In one instance the clinical picture 2 weeks after the onset of the stomatitis became one of lethargy, coma, vomiting of bile and blood-stained material, hematemesis and uncontrollable epistaxis and icterus. The histologic appearance of the liver indicated patchy necrosis of the parenchymal cells, many herpetic inclusions in the nuclei of the survivors and innumerable mitotic figures. While only a few cases of herpetic hepatitis have been recorded thus far, the true incidence of involvement of the liver in primary herpes simplex infections may be assumed to be much larger, although unrecognized, since few patients die, and few have been studied with respect to liver function.

Infectious Hepatitis. Until recently it was believed that the virus or viruses of infectious hepatitis and homologous serum jaundice did not affect young infants. Stokes and his associates[45] described hepatitis in 12 infants under the age of 2 months and in one case were able to transmit serum hepatitis from one of the infants and also from the mother to human volunteers. These workers and also Craig and Landing[9] described the pathologic findings and found the lesions similar to those seen in infectious hepatitis of older individuals. The author has seen a considerable number of similar cases in very young infants. The age of the patients made it necessary to assume that the disease was acquired by transplacental transmission. Since the majority of the mothers of such infants failed to show symptoms while, conversely, an born to mothers having known infec hepatitis during pregnancy failed to dev the disease,[30] it is believed that the responsible for the cases recognized in infants is that of homologous serum rather than of infectious hepatitis. The of homologous serum jaundice is capab persisting for years in the blood w causing symptoms.

The clinical features may resemble of viral hepatitis of later life, but the la tory tests sometimes fail to give the exp picture of disturbed liver function. In of the cases reported by Craig and La the clinical picture was that of obstr jaundice in the neonatal period with ac stools and bile but no urobilinogen urine. The liver is usually enlarged, spleen, only occasionally. The serum rubin is elevated, usually as a result of increases of both direct and indirect fract The jaundice tends to fluctuate in inte Only half of the cases show abn cephalin-flocculation and thymol turb tests. The disease has a high mortali young infants. Recovery seems to be plete in most cases, but cirrhosis has reported as a sequel. It has been sugg that some instances of familial cirrhos veloping in consecutive siblings may r sent end stages of serum hepatitis transm by a symptom-free mother harboring virus over a number of years.

The diagnosis of viral hepatitis in the few months of life is extremely di especially if the liver function tests sho gross abnormalities. Liver biopsy or exp tory laparotomy is frequently required treatment is not as yet well standardize cause of the recent recognition of the o rence of viral hepatitis in the newborn

Infectious hepatitis in older infants children is now recognized as fairly com Its etiology, general features and therap similar to those of the disease in a therefore, it is unnecessary in a book de to diseases of the liver to dwell at lengt infectious hepatitis in childhood. It is tinent to point out, however, that the rec tion of infectious hepatitis in early chil has increased with the awareness a physicians of its occurrence in this age g It has been pointed out[4] that there



200. Fulminating hepatitis in 3½-
old infant transfused at 1 month
. The symptoms were massive
g, hypoprothrombinemia, icterus,
ascites, death in respiratory
Cephalin flocculation 3+, serum
n 3.5 mg.%. The histologic pic-
that of acute atrophy. Only the bile
ave survived.

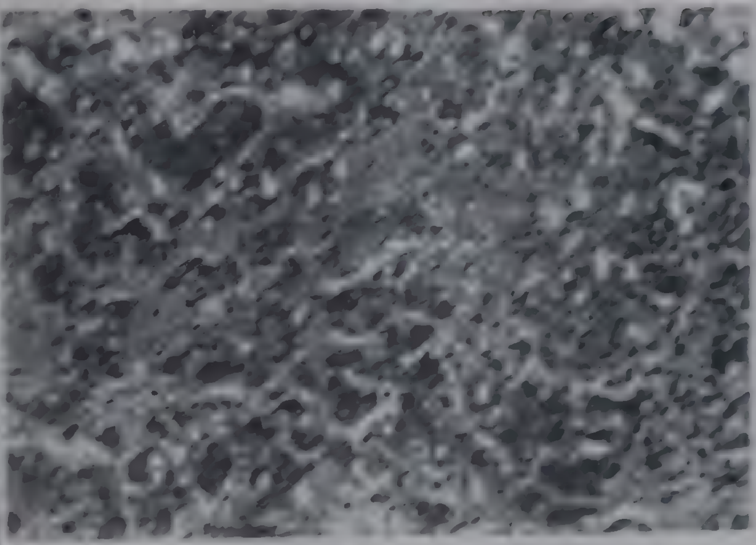


FIG. 201. Fatal acute infectious hepatitis in a 6-year-old boy dying 3 weeks after the onset of fever followed by vomiting, melena, icterus, lethargy, extreme hepatomegaly, anemia, hypoprothrombinemia and other marked abnormalities in liver function. Ascites, edema and coma supervened.

uate descriptions of the clinical and
y findings of infectious hepatitis in
ildren. The impression of most ex-
l clinicians that the disease is gen-
ld in children[25] seems to be sup-
y the paucity of published records
es. This is not to say, however, that
s hepatitis in children is invariably
Fulminating and fatal forms do
this laboratory a number of cases
hepatitis have been seen. On the
nd, the studies of Bennett[4] and his
s have established the fact that the
form of infectious hepatitis may be
antly nonicteric in early life. In a
a chronic endemic in an orphanage
26 infants with sufficient evidence
sh the diagnosis had bilirubinemia.
ence of the disease in the infants
gnized only because of an outbreak
lly manifest hepatitis among the
onnel.

Y LIVER IN INFANCY AND CHILDHOOD

psy material from infants and chil-
presence of visible fat in the polygonal cells of the liver is an extremely common finding. The extent of the fatty changes and the size of the fat droplets are highly variable. It is likely that these variations have a quantitative rather than qualitative meaning. The distinction between fatty degeneration and fatty infiltration has been

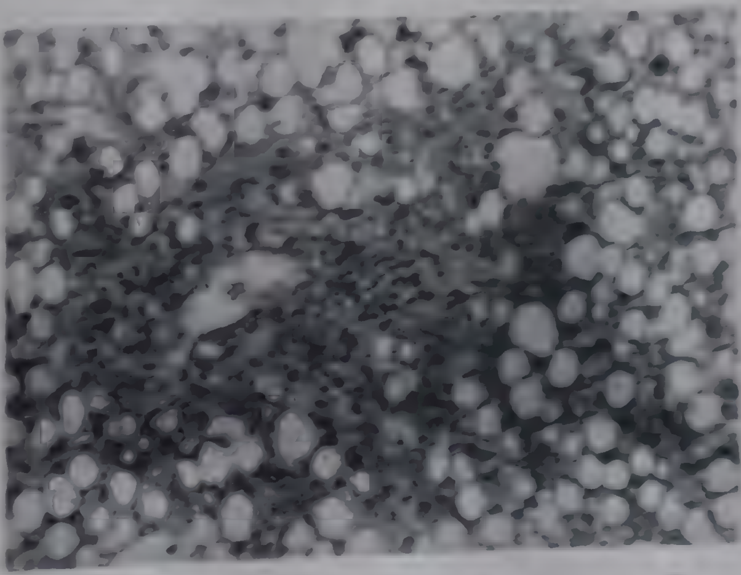


FIG. 202. Severe fatty liver. From a 5-month-old infant dying 10 days after onset of extensive bronchiolitis and bronchopneumonia. The terminal picture was suggestive of hepatic failure because of marked hepatomegaly, melena, coma, convulsions, edema and an acidotic type of breathing. The renal tubules likewise showed severe fatty changes.

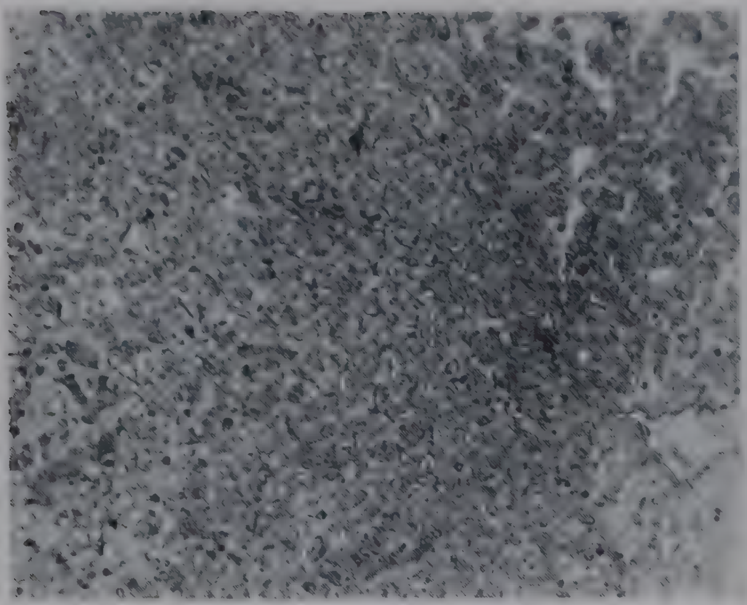


FIG. 203. Massive necrosis (confluent central and focal type) attributed to severe hypoxia in an 8-day-old infant with severe congenital heart disease, difficult delivery and cerebral hemorrhage. The patient had shown hepatomegaly, icterus and melena, as well as marked hypoprothrombinemia, during life. Serum bilirubin at 8 days 10.5 mg.%; prothrombin time 50 seconds; cephalin flocculation 3+.

largely abandoned as unreliable. What should be called fatty liver is somewhat a question of definition. In many infants dying with a variety of disease, notably infections and conditions associated with malnutrition and with hypoxia, mild to moderately severe, usually zonal or spotty fat deposits are found. As a rule, these changes do not contribute significantly to enlargement of the liver and are probably without functional or clinical significance. If only the markedly enlarged grossly pale yellow, greasy liver in which virtually every cell is distended with fat globules is designated as fatty liver, the condition is relatively rare. Among the chief causes of such fatty metamorphosis in early life—fatty hepatomegaly would be a better term—are severe malnutrition; severe prolonged infection such as generalized tuberculosis; poorly controlled diabetes with lipemia and other conditions associated with long-standing hyperlipemia; and certain poisonings, notably aspirin poisoning and carbon tetrachloride poisoning. Under the heading of malnutrition one should include not only deficiencies in dietary intake but conditions interfering with the absorption of foodstuffs, such as untreated fibrocystic disease of the pancreas. Little is known about the functional state of the liver in children with such severe states of fatty metamorphosis. Clinically, there is as a rule surprisingly little evidence of impairment in hepatic function, and the condition is recognized more often at autopsy than suspected during life. It is likely from observations in adults with comparable fatty livers[38] that such infants are subject to the hazard of sudden hepatic failure. Such a mechanism has been invoked as the cause of death in a syndrome of infants in which fatty liver is the chief pathologic finding and is designated variously as kwashiorkor infantile pellagra, malignant malnutrition and fat disease of the liver.[26] The disease is not seen in this country but has been reported from many tropical areas. It is regarded as a nutritional deficiency disease in which the basic defect lies in an inadequate protein intake. The clinical features vary presumably because of variations in the associated deficiencies in other foodstuffs Diarrhea, cheilosis, stomatitis, dermatitis fever, edema, anemia and signs of involvement of the central nervous system have been reported. The prognosis in cases sufficiently severe to reach hospitals has been extremely poor. The Gillmans[10] have reported good results with the use of hog-stomac preparations.

HEPATOCELLULAR NECROSIS

Like fatty change of minor degree, necrosis of the polygonal cells of the liver is a ver common pathologic finding in the pediatri age group but is rarely associated with clin cal manifestations or with evidence of impaired hepatic function. Most often th necrosis is focal in character and is assoc ated with various generalized infection which dominate the clinical picture. The sta of hepatic function is seldom investigate under these circumstances, but usually n impairment is demonstrable,[17] nor would be expected, since the bulk of the pa enchyma remains intact. The same state ments apply to the central type of necros as long as the lesion is not too extensiv This type of necrosis is seen likewise

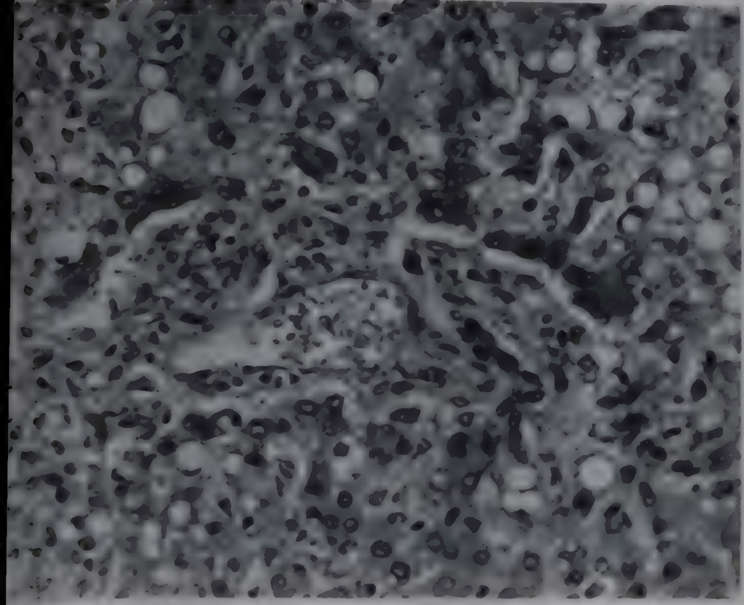


FIG. 204. Changes at the periphery of the hepatic lobules consisting of fatty metamorphosis, early proliferation of ducts and minimal infiltration with inflammatory cells. This is a common picture in severe or prolonged infantile diarrhea. Grossly, the liver was icteric in this 3-month-old infant dying of bronchopneumonia complicated by severe diarrhea.

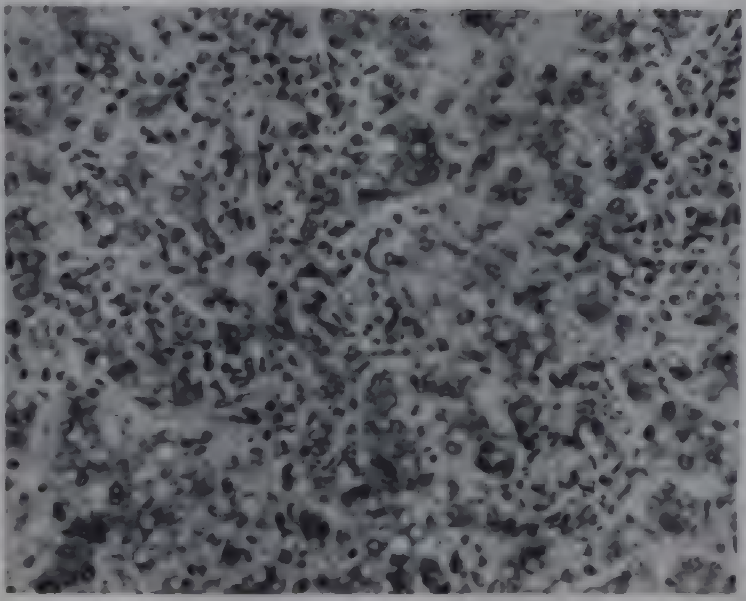


FIG. 205. More severe changes of the type illustrated in Figure 204. Note the rather severe infiltration with leukocytes. From a 6-week-old infant dying from renal insufficiency due to congenital hydronephrosis and complicated by severe diarrhea.

fectious processes not directly involving the ver, and in conditions producing severe poxia and circulatory shock. Occasionally, e necrosis becomes so extensive that patic function is compromised, and clinical anifestations arise, such as jaundice, en- rgement of the liver, abnormal bleeding and en death from what appears to be hepatic ilure. An illustrative case history is given the caption for Figure 203. Central necro- is also the type of lesion seen in poison- gs, such as carbon tetrachloride and tannic- id poisoning.[48] The once-common finding hepatic necrosis in fatal burns has become re with the discontinuation of tannic-acid erapy.

JAUNDICE AND INFANTILE DIARRHEA

The association of diarrheal disease in fancy with jaundice is not uncommon. The thologic changes described in the liver in ch cases are not constant, a fact which is rdly surprising in view of the variable and ten obscure etiologic background of infan- e diarrheas. Moreover, it is to be expected that the processes responsible for the development of icterus or of a hepatic lesion are influenced by the child's age and by the severity and the duration of the diarrhea, as well as by therapeutic measures.

Infants dying as the result of diarrheal disease frequently show fatty change and sometimes degeneration of the polygonal cells of the liver, whether or not they were jaundiced prior to death. When jaundice is present in very young infants who acquire diarrhea and become dehydrated while the functional immaturity of the liver still creates a tendency toward retention of bile, there may be no morphologic evidence of liver damage. At most one finds, especially in premature infants, the so-called bile thrombi of inspissated secretion in the intercellular canaliculi and perhaps more or less fatty change. In somewhat older infants the development of jaundice in the course of diarrhea is of more serious import and is more likely to be associated with definite histologic lesions. Occasionally, these lesions have the appearance of infectious hepatitis, and one is forced to assume that the diarrhea was merely a manifestation of that disease. Usually, however, the hepatic lesion is of a different type and appears to be secondary to the diarrhea. The changes involve chiefly the periportal

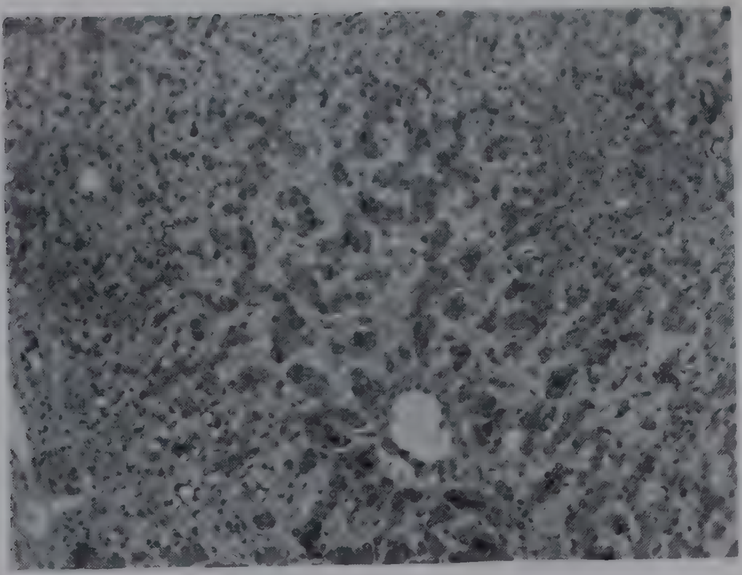


FIG. 206. A still more advanced stage of the lesions shown in Figures 204 and 205. The lobules are surrounded by wide bands of fibrosis; the newly formed fibrous tissue is infiltrated by leukocytes; the polygonal cells at the periphery have undergone fatty changes and necrosis; the central portions show atrophy and marked inspissation of bile. From a 2-month-old infant with vomiting due to a congenital peritoneal band. The infant acquired severe diarrhea and became distended, dehydrated and icteric.

zones of the lobules and range from fatty metamorphosis to necrosis of liver cells with an accompanying proliferation of bile canaliculi, periportal edema, sometimes fibrosis and inflammatory cell infiltration. The subject was restudied recently by Wainwright,[46] who described this picture under the title of hepatitis associated with infantile diarrhea. However, he recognized the fact that the same changes may occur in conditions other than diarrhea, and this has been the experience in the author's own laboratory. Despite the similarity of the lesions to cholangiolitis in adults, Wainwright believes the lesions to be of toxic origin. Prognostically, the appearance of jaundice generally is an unfavorable sign in the presence of diarrhea or other infections. Apart from the general measures indicated by the primary disease, the administration of protein by the oral or the parenteral route, of vitamins of the B group and of potassium and sodium as indicated by electrolyte studies has been advocated.[41]

INFANTILE AND JUVENILE CIRRHOSIS

Various types of hepatic cirrhosis morphologically identical with those seen in adults are encountered in infants and children. Very little is known about etiologic factors in the juvenile cirrhosis, and this ignorance is reflected in the confusing nomenclature, in the mixture of morphologic, descriptive and etiologic terms used in various classifications, in the fact that almost every author has found it necessary to construct or adapt his own classification, and in the large residue of "juvenile atrophic" and "idiopathic" cirrhoses found in the literature. Moreover, it must be admitted that the morphologic distinction between certain types of cirrhosis, notably portal and post-necrotic cirrhosis, is often difficult, and somewhat arbitrary assignment of individual cases to one or the other category is often necessary. Many authors reporting chiefly in the pediatric literature actually have avoided the attempt to classify the type of cirrhosis.[51] In spite of this unsatisfactory state of affairs it is possible to characterize the cirrhoses of early life by certain general statements.

1. The incidence is very much lower than cirrhosis in the adult. Juvenile cirrhosis is a rare disease, although perhaps not as rare as was believed formerly. Keller and Nute[31] found 40 cases proved histologically and several additional cases clinically diagnosed but not proved among 82,866 admissions to a Children's Hospital. The author's own material includes 26 cases of all types proved by autopsy in a 12-year period encompassing approximately 3,000 autopsies of infants and children from 0 to 12 years of age. There appears to be no predominance of males over females among affected children.

2. In contrast with adult cirrhosis, the portal (Laennec type) is not the predominant type. Various forms of biliary cirrhosis and postnecrotic cirrhosis appear to be relatively common.

3. The etiologic factors, known and unknown, differ from those prevailing in cirrhosis of later life. In early infancy obstructive biliary cirrhosis is most commonly the result of congenital atresia of the bile

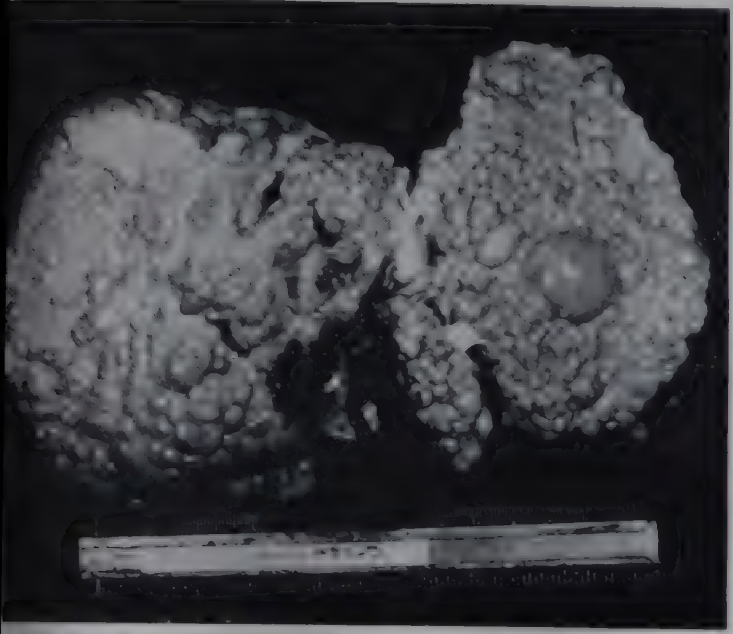


FIG. 207. Coarse nodular cirrhosis in a 6-year-old boy with de Toni-Fanconi syndrome.

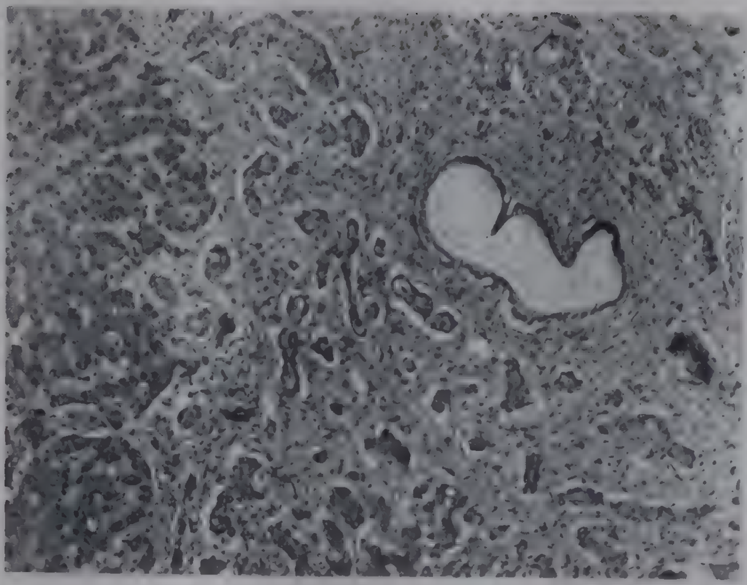


FIG. 208. Obstruction of intrahepatic bile duct with inspissated secretion in a 3-year-old child dying of pancreatic fibrosis (mucoviscidosis). Note dilatation of a larger duct with mucouslike secretion and proliferation and fibrosis about smaller ducts, some of which are also filled with inspissated secretions.

ucts. As mentioned earlier, the cirrhosis due
the hepatic damage associated with eryth-
oblastosis fetalis is uncommon.[8] Before
e advent of Rh and of adequate diagnostic
ethods many conditions showing normo-
lastemia and extramedullary hemopoiesis in
oung infants were labeled erythroblastosis
talis on hematologic or pathologic grounds
ow known to be inadequate. Moreover, the
evelopment of various hepatic lesions in
fants repeatedly transfused during the new-
orn period might in some cases be the result
f the introduction of viral agents such as the
irus of homologous serum jaundice which,
uperimposed on the hepatic changes caused
y the primary disease, might well produce
rrhotic changes. Since the introduction of
rologic methods for the diagnosis of ery-
roblastosis fetalis the author has not seen a
se of cirrhosis attributable to that condition
one, although this is not to deny the possi-
ility of such an occurrence.

Viral and other infectious agents undoubt-
dly can be the cause of cirrhosis in infancy.
ention has been made of the diffuse intra-
bular fibrosis and cirrhosis following he-
atic involvement in cytomegalic inclusion
sease. The similar lesion found in congeni-
l syphilis is well known. To what extent cir-
osis in infancy and childhood may follow
fections with the viruses of infectious hepatitis is not known. The suggestion has been made that some cases of familial cirrhosis in children may have their origin in viral hepatitis transmitted transplacentally by a carrier of the virus of homologous serum jaundice.[18] Bacterial infections capable of producing extensive hepatic necrosis, and liver poisons also have been incriminated.

4. Familial occurrence of juvenile cirrhosis is not uncommon and is in itself a significant and striking fact. Granting the possibility of viral infections transmitted by the mother, it is likely that genetic features are involved in the majority of cases of familial cirrhosis. Such factors probably do not produce cirrhosis of the liver but determine general metabolic abnormalities which secondarily lead to liver damage and cirrhosis. A number of such heredofamilial conditions are known in addition to Wilson's hepato-lenticular degeneration. Among these are Gaucher's disease and Niemann-Pick's disease and galactosemia. The coarse nodular cirrhosis sometimes seen in the de Toni-Fanconi syndrome falls into the same group. In this condition, characterized by cystinosis and amino-aciduria, glycosuria and hypophosphatemic refractory rickets, deposits of cys-

tine form, which seem to be responsible for extensive changes in the liver, the kidneys and the reticuloendothelial system.

A different, although likewise genetically induced mechanism, accounts for the cirrhosis sometimes seen in pancreatic fibrosis and first described by Farber[14] in support of the mucoviscidosis theory of that condition. One frequently finds focal areas of extensive periportal fibrosis secondary to obstruction of the small bile ducts with an eosinophilic secretion in cases of fibrocystic disease of the pancreas. In rare instances this process is extensive enough to produce a generalized cirrhosis.

The role of nutritional factors in infantile cirrhosis is not clear. The high incidence of juvenile cirrhosis reported from India has been interpreted as evidence of a dietary background, but conclusive proof is lacking.

The clinical course of cirrhosis in infants and children is not much different from that in adults. It depends, of course, somewhat on the type of lesion. Among children with portal cirrhosis splenomegaly is very common. The prognosis in cases not amenable to surgical correction is generally poor. Therapy has been in keeping with that used by the internist. A high-protein diet, adequate vitamin intake and the appropriate use of diuretics, transfusions and paracentesis have been the chief pillars of treatment. The use of intravenously administered liver extracts has not yet been evaluated in infantile cirrhosis.

The diagnosis of cirrhosis in infancy and childhood offers peculiar difficulties and challenges. It requires first of all an awareness on the part of the physician of the occurrence of the disease and of its varied background. The clinical symptoms are more variable than in the adult because of the frequent association of cirrhosis in childhood with systemic diseases. Longstanding or recurrent icterus, hepatomegaly, splenomegaly, failure to gain and to grow, anorexia and anemia are common. Ascites, distention of the abdominal veins, edema, fever and hemorrhage are manifestations of fairly advanced disease. The demonstration of abnormal liver functions will increase the suspicion, but often a biopsy is required to establish the diagnosis. Reducing substances found in the urine in suspected cases of juvenile cirrhosis are likely to be glucose, but their nature mus be verified in order to exclude galactosemia, a condition responding to the elimination o lactose from the diet. Bone-marrow aspiration may disclose the characteristic cells o Gaucher's or Niemann-Pick's disease, or the crystals of cystine found in the reticulum cells in the Fanconi syndrome. Family history and, in some instances, the study of blood groups and maternal antibodies may be important. The physician should not be satisfied with the diagnosis of hepatic cirrhosis in a child but should make every effort to establish the associated or underlying condition, even though this will not be possible in every case.

NEOPLASMS OF THE LIVER IN CHILDHOOD

Primary hepatic tumors are rare in this age group. Relatively frequent types are the primary carcinoma, the benign hepatoma or hamartomas and the hemangioma.

Primary carcinomas have been classified according to histologic structure as hepatomas and cholangiomas. In childhood the liver-cell type appears to be the commoner of the two. Clinically, there appears to be no important difference between the two types. Primary carcinoma has been reported in newborns and very young infants and evidently can develop during fetal life. The tumors, when seen at operation or at autopsy, are often multiple, and then it is usually impossible to decide whether they were originally single with multiple intrahepatic metastases or had a multicentric origin. They tend to metastasize to the lymph nodes of the portal area and the mediastinum, the lungs, the pleura and the pericardium and may extend by direct invasion into the portal vein or the inferior vena cava.[44] The clinical course is usually rapid but is often lacking in characteristic symptoms such as ascites or jaundice. Digestive disturbances, abdominal discomfort, anorexia, vomiting, weight loss, anemia and cachexia are frequently observed. The liver becomes enlarged, sometimes enormously, and may be nodular if the growths have reached the surface. The prognosis is almost uniformly poor, but in the absence of demonstrable metastases exploration is indicated, and resectable tumors should be excised.

Benign Solitary Hepatomas or Hamartomas. A far better outlook is associated with the benign solitary hepatomas or hamartomas, which some authors regard as developmental anomalies rather than as true neoplasms. However, some of these tumors may become malignant. Removal has been followed by complete cure.[5] The tumors may be pedunculated or may be deeply embedded in the substance of the liver. They cause symptoms chiefly by pressure on the adjacent liver tissue itself or on the neighboring viscera.

Hemangiomas are often small multiple congenital lesions found incidentally on inspection of the liver. Larger solitary cavernous hemangiomas, on the other hand, may cause pressure symptoms or even rupture, giving rise to massive intra-abdominal hemorrhage. The treatment for accessible solitary tumors is surgical. Multiple hemangiomas require x-ray therapy. These tumors are usually palpable[42] and occasionally compressible.

HEPATOMEGALY

The conditions causing enlargement of the liver in infants and children are legion. For the most part they do not represent primary or localized disease of the liver itself but involve this organ as the result of a distant or generalized process. In most instances the reason for the hepatomegaly is clear or at least can be suspected from the history, the general clinical picture, the blood picture or other laboratory findings. Hepatomegaly secondary to cardiac failure, to blood disorders such as erythroblastosis fetalis, other hemolytic anemias, leukemias, Letterer-Siwe's disease and the like rarely presents a diagnostic problem. This is true also of infectious processes involving the liver or affecting its size, such as generalized histoplasmosis, malaria, acute septicemias and certain viral infections including infectious mononucleosis. A more difficult diagnostic task is created by cases in which systemic manifestations are lacking and hepatomegaly is an isolated finding or is associated with splenomegaly in a child who otherwise appears to be normal. It is important that such cases be diagnosed properly, even if a laparotomy or liver biopsy should be required to reach a diagnosis. When hepatomegaly is accompanied by splenomegaly and the usual diagnostic procedures have been exhausted the possibility of one of the lipoid storage diseases, Gaucher's disease or Niemann-Pick's disease should be considered. The presence of the characteristic cells in preparations of aspirated bone marrow usually establishes the diagnosis. In the absence of splenomegaly a markedly enlarged liver which cannot be accounted for by cardiac, hematologic or infectious disorders is likely to indicate one of the following conditions: fatty liver, glycogen disease, parasitism or neoplasm.

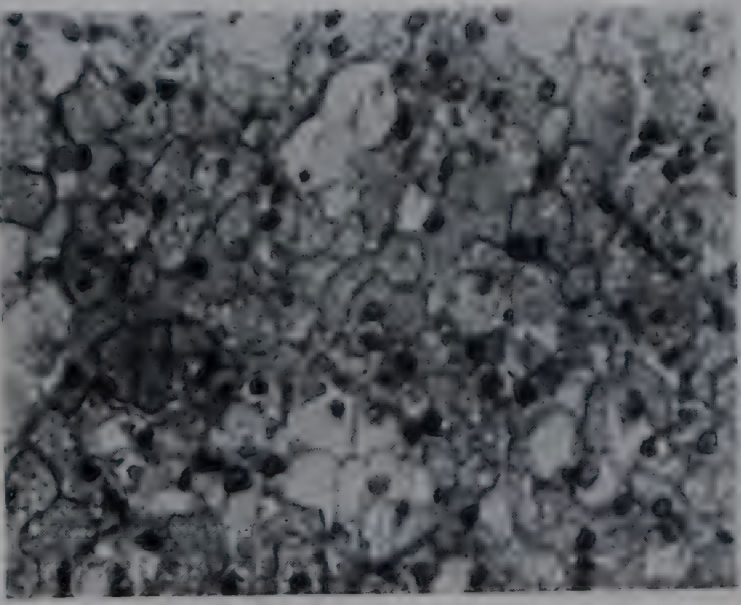


Fig. 209. Liver in Niemann-Pick's disease. Note large foam cells in sinusoids, but also enlargement and plant cell-like contours of polygonal cells.

Fatty liver has been discussed above. The hepatic type of glycogen storage disease produces enormous enlargement of the liver. The abnormality appears to reside in a faulty enzyme system. The synthesis of glycogen seems to proceed normally, but the conversion of glycogen to glucose is impaired or altogether lacking. As a result, glycogen accumulates in the polygonal cells, and glucose is unavailable to the body at large. The patients characteristically show fasting hypoglycemia yet a diabetic type of response to carbohydrate-tolerance tests, failure of the blood sugar to respond to adrenalin, ketonuria and retardation of growth. The condition is determined genetically, and several siblings

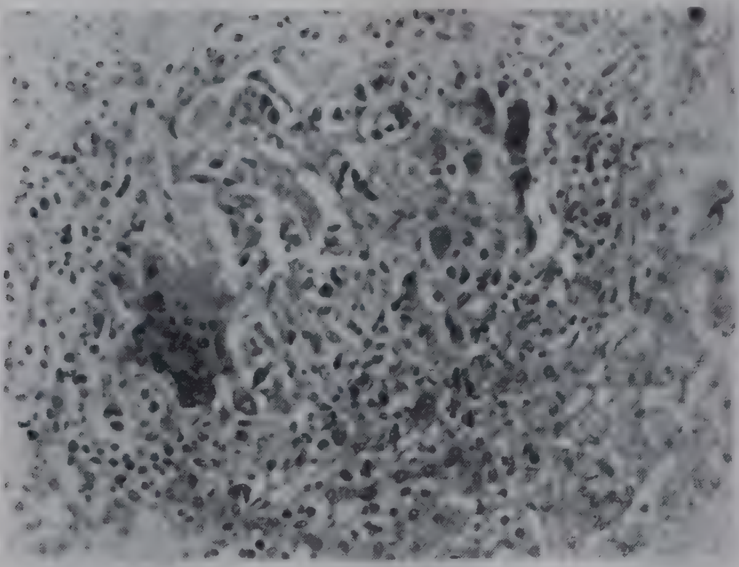


FIG. 210. Granulomalike lesion in liver from a 3-year-old child with marked eosinophilia and hepatomegaly.

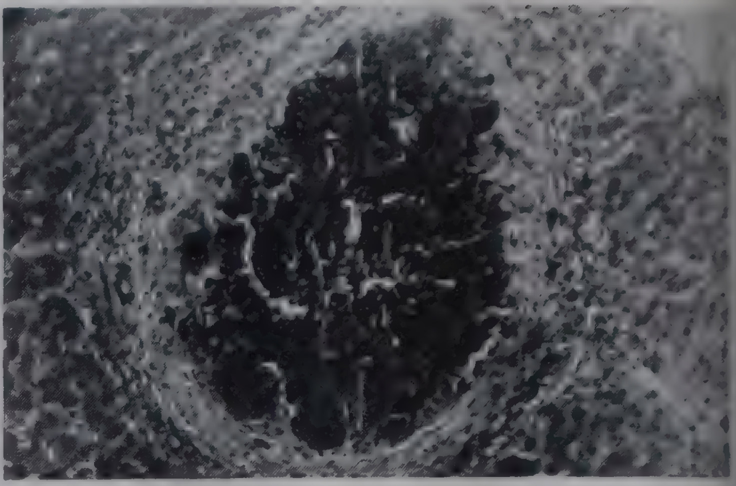


FIG. 212. Healed stage of lesions shown in Figures 210 and 211, walled off and calcified. Numerous active lesions were present at the same time.

in a family may have the disease. Glycogen storage disease is said to improve as the patient reaches puberty. The diagnosis is not difficult in the presence of an enormously enlarged liver, the characteristic laboratory findings and in the absence of splenomegaly and icterus. Frequently, liver biopsy is performed, although, one suspects, often more for reasons of scientific interest than of diagnostic necessity. Since the muscle glycogen is likewise increased, muscle biopsy can be used to confirm the diagnosis.

Parasitic involvement of the liver is relatively rare in this country, and such diseases as schistosomiasis need not be considered here. Recently, it has become clear, however, that another parasitic syndrome involving chiefly the liver of young children is not at all uncommon in this country. The chief manifestations of this syndrome are hepatomegaly and marked eosinophilia.[55] Occasionally, there may also be slight splenic enlargement. The condition may be asymptomatic, but frequently the patients show various manifestations suggesting allergy, such as urticaria or fleeting joint pains. The eosinophilia reaches tremendous degrees with elevation of the total white blood count as high as 100,000 to 120,000 and as many as 80 per cent eosinophils. Indeed, the diagnosis of eosinophilic leukemia formerly was often made in these children. The pathologic findings are those of eosinophilic abscesses and granulomas scattered throughout the liver. Recently, Beaver and his associates[3] have demonstrated larvae of canine ascaris in such lesions and have designated the disease as a visceral form of larva migrans resulting from the ingestion of the ova. The condition affects predominantly young children about the age of 2 to 3 years, and a history of dirt-eating is almost always obtained. The laboratory findings apart from the eosinophilia are often not characteristic. Impaired hepatic function is not usually demonstrable, but frequently a marked hyperproteinemia due to a large increase in the serum globulin is demonstrable. The prognosis appears to be good, although both hepatomegaly and eosinophilia may persist for months and years. No efficacious therapy

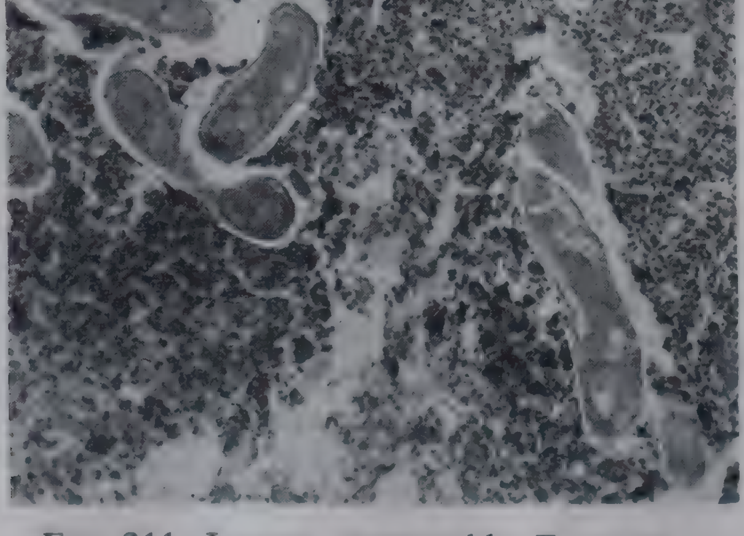


FIG. 211. Larvae, presumably *Toxacara canis*, in eosinophilic abscess of liver.

as been described, but as a rule there is o need for treatment.

Neoplasms primary in the liver have been iscussed. Diffuse hepatic enlargement may e the first sign of metastatic involvement by ne of the commonest malignant neoplasms, *euroblastoma*. Widespread dissemination of netastatic foci, usually from a primary site n the adrenals, may lead to marked hepaomegaly in seemingly healthy infants. The rimary tumor may not be demonstrable by physical examination. Neuroblastoma always should be suspected in the presence of unexplained hepatomegaly in infants and young children. If no other metastases are found, the intravenous pyelogram may show the primary tumor. Failing this, an exploratory laparotomy is indicated. This is not an academic diagnosis, since it has been shown that neuroblastoma may be cured permanently, even when multiple metastases to the liver have occurred.[52]

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Chapter 24

PARASITIC DISEASES OF THE LIVER

Enrique Koppisch, M.D.

Of the metazoan parasites or helminths those which may damage the liver are *Ascaris lumbricoides, Echinococcus granulosus,* and the flukes. The latter are represented by 5 genera and 7 species: The schistosomes (*Schistosoma haematobium, S. japonicum* and *S. mansoni*), and *Fasciola hepatica, Clonorchis sinensis, Opisthorchis felineus* and *Dicrocoelium dendriticum.*

ASCARIASIS

The hepatic and biliary complications of ascariasis are so rare as to call only for mention. They consist in the penetration of the choledochus, the larger intrahepatic bile ducts, and even the gallbladder and the main pancreatic duct, by ascarids entering through the papilla of Vater. This results in biliary obstruction and in acute inflammation of one or more of those parts, at times with the formation of hepatic abscesses or acute pancreatitis. The clinical problem in these cases is that of an acute surgical abdomen, with localization in the upper portions, mostly in the right upper quadrant, and with obstructive jaundice. With such a clinical picture, ascariasis always should be thought of if there is a history of the frequent passage of ascaris worms per rectum, or if fecal examinations indicate a large worm load. It is important to remember that these acute manifestations are apt to arise within the first 24 hours after administration of a vermifuge.

SCHISTOSOMIASIS

EPIDEMIOLOGY

The infection is acquired by bathing in, or wading through, infested ponds, streams, or irrigation canals. The urinary form occu in Africa mostly; the Asiatic, in the Fa East; and the mansonic, in Africa, certai parts of the Antilles and the northern par of South America (Venezuela, the Guian and northern Brazil).

LIFE-HISTORY

The fork-tailed cercariae enter throug the skin, losing the tail in that process an becoming metacercariae. The latter ente lymphatics in the derma, pass through r gional lymph nodes, and presumably up th cysterna chili and the thoracic duct, thu reaching the veins. They then pass along th pulmonary circuit from the right side of th heart to the left and enter the general circulation. It seems that only those that are abl to pass from the arterial to the venous sid are able to survive, and that this must tak place in abdominal organs drained by th portal system. So far as is known, they ca mature only in intrahepatic portal vein where each metacercaria becomes an adu male or female worm. This occurs from 3 to 60 days after penetration of the cercaria in the case of *Schistosoma haematobiu* from 37 to 42 days in the case of *S. manson* and from 30 to 45 days in that of *S. japonicum.* The adult worms then travel again the stream of the mesenteric circulatio where the adults copulate, and ovipositio takes place in urinary plexuses (*S. haem tobium*), and in mesenteric, colic an hemorrhoidal veins (*S. japonicum* and *mansoni*).

PATHOGENESIS AND PATHOLOGY

The eggs are laid in narrow venules the submucosa of the intestine and the ur nary bladder, according to the species. Thos

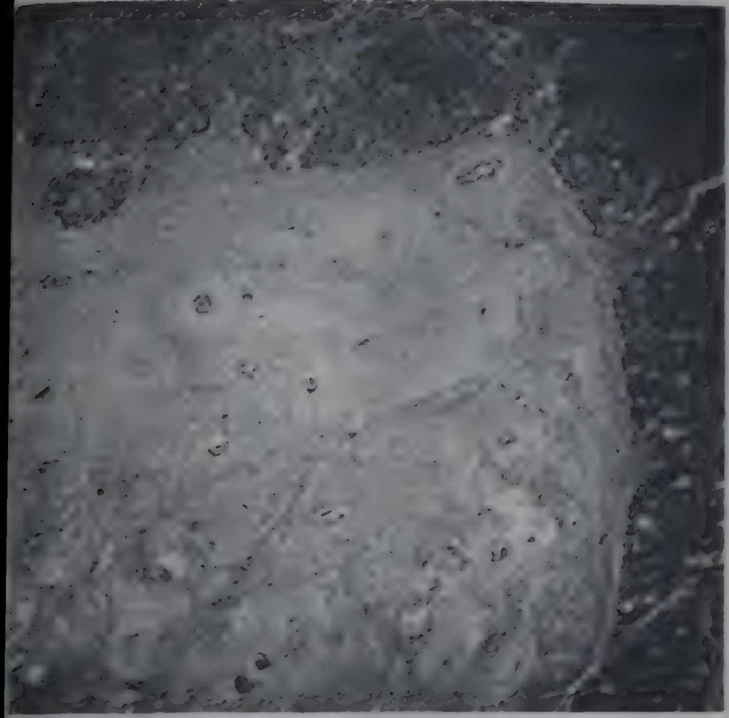

FIG. 213. Marked portal fibrosis and formation of multiple pseudotubercles in Manson's schistosomiasis. (× 21)

t retained in those tissues, or those that e not extruded with the urine or the feces, e swept back passively into the liver, where ey accumulate in the portal spaces.[4, 8] This ts up the formation of pseudotubercles out eggs and a progressive portal fibrosis igs. 213, 214), with portal hypertension. about 20 per cent of the more severe ses this fibrosis is mostly about the larger rahepatic portal branches, producing the -called Symmer's[15] white clay pipestem pe of fibrosis which, so far as is known, curs in no other disease. In the rest of ses the cirrhosis is of the Laennec type. schistosomiasis, however, the surface of e liver is usually only slightly nodular and t hobnailed. Microscopically, formation of eudolobules and proliferation of bile ducts e not as marked as in idiopathic cirrhosis. n the other hand, changes have been de- ribed[11] recently in the intrahepatic portal anches that should be of aid in histo- thologic differentiation: a granulomatous ansformation of the wall, and obliterative anges in the lumen. In old, inactive cases, nsiderable discrimination is necessary in tablishing the diagnosis in biopsies or in stmortem sections, because eggshells be- me dissolved in the tissues. Only a few ay be found in cases in which oviposition s stopped or ceased to be active a long time before the liver is examined by biopsy or at autopsy.

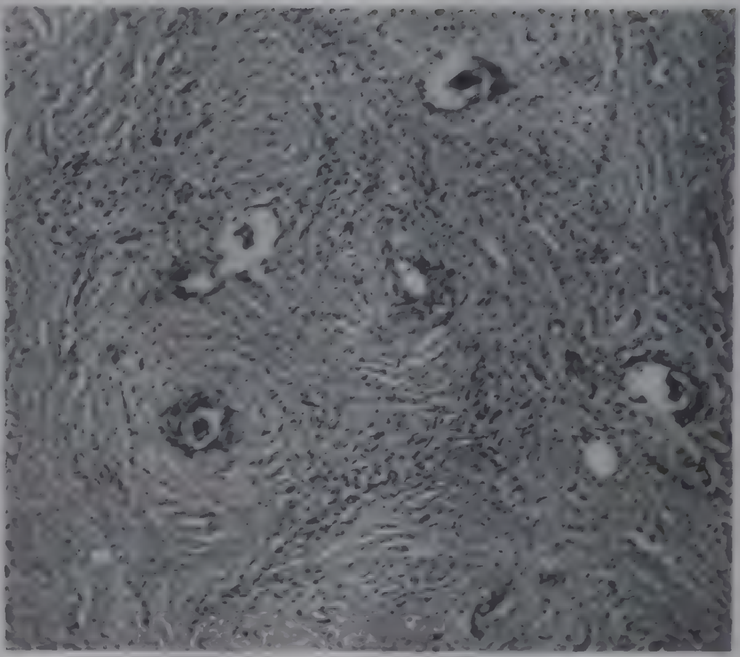

FIG. 214. Detail of Figure 213. (× 80)

As the portal fibrosis increases, the spleen enlarges, and gastro-esophageal varices develop. Ultimately, the spleen may show a diffuse fibrosis of the pulp and a diminution in the size and the number of lymphoid follicles. Rupture of esophageal varices may result in anemia or may be the direct cause of death.

SYMPTOMS AND SIGNS

By the time that evidence of liver damage becomes apparent, the signs and symptoms will be those of a Laennec type of cirrhosis or of a late Banti's syndrome.[14] It usually takes over 10 years after a single heavy exposure, or after repeated exposures, to develop evidences of cirrhosis. Some authors[3] doubt that the schistosomes possess the capacity to produce cirrhosis; they believe that hepatic damage in these cases is the result of nutritional deficiency. In Puerto Rico,[9] a review of 1,000 consecutive autopsies has yielded a general incidence of cirrhosis of 7.5 per cent. Among 860 of that series that were not infected with Manson's schistosomiasis, the incidence was 5.7 per cent, while among 140 cases of schistosomiasis, cirrhosis was found in 18.5 per cent.

Before the development of hepatic cirrhosis the disease is manifested by recurring attacks of diarrhea in bouts of a few days' duration. The only feature suggestive of schistosomiasis is the frequent presence of visible blood in the stools, together with eosinophilia. After a number of years the picture becomes that of hepatic cirrhosis. In the late stages the diagnosis may be difficult or impossible, since the blood may show no eosinophilia, and eggs may not be found in the stools. In about one fourth of the fatal cases death is due to rupture of esophageal varices; in another fourth it is due to cachexia and cirrhosis, while the remaining half succumb to hyperinfestation, complications or intercurrent disease.

Since the symptoms and signs are in no way different from those of Laennec's cirrhosis, they will not be discussed. In young adults, and even in preadolescent children of both sexes, enlargement of the spleen and the liver, when it is persistent and unaccompanied by fever or jaundice, requires careful investigation as to the possibility of a schistosomal cause, provided, of course, that infestation is geographically possible in the particular case. The importance of early diagnosis in such cases would lie in the prevention, by means of appropriate treatment, of further damage to the liver.

DIAGNOSIS

This depends mainly on awareness of the occurrence of this disease, as well as knowledge of the endemic geographic foci. In the case of urinary schistosomiasis, due to *S. haematobium,* the signs and symptoms are primarily genito-urinary, so that from a practical point of view the present discussion limits itself to the mansonic (*S. mansoni*) and the Asiatic (*S. japonicum*) forms.

A history of itching of the skin after exposure to infested water should be suggestive. The itching involves the parts of the skin exposed to the water and comes on while in heavily infested water, when the exposure has been of more than a few minutes' duration. Itching may begin within a half hour after the subject comes out of the water.

The laboratory diagnosis hinges on the identification of ova as the most reliable criterion and on serologic tests that are helpful in certain cases but not entirely reliable for thorough assessment of each case, with the exception of the circumoval precipitation test.

In *S. haematobium* infections the urinary sediment obtained by centrifugation at 2,000 to 5,000 r.p.m. is examined microscopically. In the mansonic and the Asiatic forms the feces can be examined by the direct smear method, which is reliable only in heavy infections. Usually, methods of concentration must be resorted to, such as that of Weller and Dammin,[16] as modified by Hunter et al.[7] Not less than 10 or 15 examinations in the course of 1 or 2 months should be carried out before deciding that a suspicious case is not passing ova.

The best diagnostic method is that of biopsy of small snips of mucosa[13] of the urinary bladder for *S. haematobium* and of the rectal mucosa for the mansonic and the Asiatic forms. For the latter two this is done best on the transverse rectal folds (valve of Houston). The removed portion is softened by placing it in distilled water for about 5 minutes and is compressed firmly between two glass slides for direct examination under the microscope; the search is directed toward the relative number of empty egg shells and eggs with embryos, and for species identification.

Among the serologic tests there is fixation of complement, with cercarial and adult antigens. Intradermal reactions can be carried out with antigens also obtained from cercariae or adult worms. These tests, in proper hands, are highly diagnostic and yield but few false positives. Even so, they cannot be considered as practical in other than specialized laboratories. Furthermore, their clinical evaluation must be conducted with great care and as a part of a thorough study, for a positive test by itself means nothing so far as activity of the infection is concerned. Positive serologic and intracutaneous tests, when no eggshells (or only empty ones, calcified or not) are found in the stools after 10 or 15 examinations, and when there is no eosinophilia, would mean an inactive infection. Such a result would not be an indication for specific treatment.

Under such circumstances not even needle biopsy of the liver should be considered. Needle biopsy is the last resort in diagnosis he writer's needle biopsy material, scanty it is, leaves him with the impression that e amount of hepatic tissue removed is so anty that in clinically doubtful cases an nportant proportion of these will fail to eld the only reliable diagnostic feature: hole eggs or fragments of shells. Fibrosis the portal spaces with little or no proferation of bile ducts, little or no formaon of pseudolobules, and eosinophilic inltration are suggestive but not diagnostic.

A recently developed and very promising rocedure is the circumoval precipitation est.[12] Fresh, experimentally obtained, living ggs are incubated in the patient's serum at 7° C. for 8 to 10 hours. In positive reacons, transparent, well-defined, fingerlike reamers are seen extending outward, nore or less perpendicular to the eggshell. uch a result is interpreted as signifying acvity of the schistosomal infection. Furthernore, the antigen is species-specific, e.g., if ne serum is from a case of the mansonic orm, only the eggs of *S. mansoni* will yield ne reaction.

TREATMENT

In cases of proved schistosomiasis, or of uspected schistosomal involvement of the ver, with or without evidences of cirrhosis, pecific treatment is clearly indicated.

Although it is generally accepted that otassium antimony tartrate (tartar emetic) s the most effective agent, in practice Fuain (sodium antimonyl III bis-catechol-2,4 isulfonate heptahydrate) has replaced it lmost completely. Fuadin is distinctly less oxic, and since it is injected intramuscuarly, it avoids the well-known hazards of he intravenous injection of tartar emetic. It s given as follows, into the gluteus maxinus, in the case of adults: first day 1.5 ml.; econd day, 3.5 ml.; third day, 5.0 ml.; folowing with 5.0 ml. on alternate days from he fifth to the fifteenth day. This is a total f 9 injections of 40 ml. in 16 days. The J. S. Army has recommended 16 injections vith a total of 75 ml. of the injectable olution. Hernández Morales[5] recommends a otal of 120 cc. of Fuadin in doses of 5 cc. ach, on alternate days.

Probably not more than 60 to 70 per cent of cases are permanently cured by a first course of treatment. If a first course fails, it is variously recommended to follow it with either tartar emetic or anthiomaline (trivalent antimony lithium thiomalate). Tartar emetic is given intravenously in 0.5 per cent solution, as follows: first day, 8 cc., third day, 12 cc., ninth to twenty-ninth day, on alternate days, 24 cc. Anthiomaline is given intramuscularly, in doses of 3 ml. of the solution every other day, to a total of 45 cc.

ECHINOCOCCOSIS OR HYDATID DISEASE

EPIDEMIOLOGY AND LIFE-HISTORY

The adult *Echinococcus granulosus* is only 3 to 6 mm. long as it lives attached to the mucosa of the small intestine of the dog, its definitive host. The eggs pass out with the feces of this animal; when swallowed by the intermediate hosts—man, hogs, cattle and sheep—an onchosphere is liberated in the duodenum. It usually penetrates venules, so that the onchospheres are first filtered out of the portal vein in the liver, which explains why in 70 per cent of the cases the cysts develop in this organ. In some countries, as South America, most of the cysts are pulmonary, which may mean that the onchospheres can penetrate lymphatics also, then passing to the left subclavian vein, and so to the lungs. A few onchospheres manage to pass along the pulmonary circulation to the systemic, so that a few cysts at times appear in various organs and tissues.

Wherever they settle, if the onchospheres survive, they grow slowly into cysts that contain large numbers of scolices, each one representing the head of a future taenia. The cycle is completed when a dog (also wolves, jackals and coyotes) swallows the cysts contained in offal, mostly of sheep. The cyst represents the larval stage, the scolices being the infecting agent.

The disease occurs mostly in South America (from southern Brazil to southern Argentina), northern and South Africa, southern Australia and New Zealand, central and southern Europe and the Balkans, northern China and a broad belt in central

Asia. Rare cases appear in the United States and southern Canada.

Man usually acquires the disease as a child, from fondling dogs. The infection is kept up among sheep and hogs, which act as the reservoir of the larval cysts.

Pathology and Symptomatology

As regards the liver, two forms may occur in it. One of these is the *unilocular cyst,* composed of 3 layers: (1) an inner *germinative* or *embryonic membrane,* visible only with the microscope, and (2) a white, soft *cuticular* or *laminated layer,* easily separable from (3) the outer *adventitial layer,* dense and fibrous, formed as a capsule by the tissues of the host. The contents consist of limpid, watery fluid with a very fine sediment (*hydatid sand*) made up of scolices and hooklets detached from the embryonic membrane. These cysts grow slowly; generally they do not manifest themselves until after 5 to 20 years.

The passage of hydatid fluid into the host's circulation may give rise to marked eosinophilia in the peripheral blood or to urticaria or angioneurotic edema. Subperitoneal cysts in the liver may rupture, spontaneously or traumatically, into the peritoneal cavity, which constitutes a dangerous complication. If the amount of contents thus spilled is scanty, multiple secondary cysts will be implanted on the peritoneum, growing from the released scolices. When the amount of spilled content is large, anaphylactic shock, which may be fatal, may result.

The cyst may cease growing when it undergoes collapse of the laminated and embryonic layers, with resorption of the fluid and slow fibrosis, at times with calcification. Or it may become infected with pyogenic bacteria, undergoing suppuration and producing acute symptoms.

Otherwise, the signs will be those of a slowly growing mass, and the symptoms will depend mostly on evidences of compression of neighboring structures.

The second form of the disease in the liver is the *alveolar hydatid.* For some unknown reason, the liver in some cases fails to produce an adventitial layer, and the germinative and laminated layers grow diffusely among liver cells in a progressive fashion, acting both clinically and pathologically as a malignant hepatic tumor.

Diagnosis

The history of the case, as to chances of exposure and symptoms, is of great importance, and x-ray studies may be helpful. If the cyst is so situated in the liver that it can grow without compressing important structures, the condition may go unnoticed for years.

Once suspicion is aroused as to the presence of the disease, the intradermal test of Casoni, later modified by Dew, Kellaway and Williams,[2] may be of value. The antigen consists of hydatid fluid. A positive reaction is revealed as a wheal developing within 30 minutes after injection and indicates past or present infection. The precipitin test and complement-fixation reaction, if positive, in addition to the intracutaneous test, enhance the possibility of the disease being active. Whenever a cyst is excised, if it is well preserved at the time, the gross and the microscopic appearances are characteristic, and the presence of daughter cysts, scolices and hooklets in the fluid will confirm its hydatid nature.

Treatment

Hepatic cysts, which can be single or multiple, require surgical treatment. For further details consult the bibliography.[1, 10]

FASCIOLIASIS

Epidemiology and Life-History

Fasciola hepatica, one of the liver flukes, affects man mostly in sheep-raising countries, but sporadic cases are seen in many parts of the world.

The adult parasite inhabits the choledochus and the intrahepatic bile ducts. The operculated eggs are excreted with the stools and mature in fresh water. A miracidium is hatched that invades a snail, from which cercariae are produced, and these, instead of swimming freely like those of the schistosomes, form cysts attached to aquatic vegetation. Most of the infections are acquired by the eating of water cress.

PATHOGENESIS AND SYMPTOMATOLOGY

Upon ingestion, metacercariae are libered in the upper small intestine of man, and e parasites travel directly through the perineal cavity and the hepatic tissues to the ile ducts. In very heavy infections this may ve rise to extensive hepatic necrosis.

In most cases the parasites settle in the ile ducts and produce an epithelial hyperlasia, a periductal infiltration with eosinohils, lymphocytes and plasma cells, and brosis about the ducts. The ducts undergo ilatation. The worms at times penetrate ırough the wall of ducts, and form abscesske cavities in the adjacent hepatic tissue.

The symptoms are variable. There may e exacerbations of fever with leukocytosis nd various gastro-intestinal disturbances. light fever may occur during prolonged eriods. The symptoms and signs at times re those of cholecystitis or cholangitis, with ain in the right upper quadrant. Intermitnt periods of jaundice may appear. Eosinphilia may be present, and the general ealth often becomes affected. Rare cases ave been described resembling cirrhosis.

DIAGNOSIS

This is established by finding the eggs in the feces or in duodenal contents. They are readily recognizable, being large, ovoid, hyaline, with a small terminal operculum, and a size of 80 by 150 microns.

TREATMENT

Emetine hydrochloride (40 mg. intramuscularly, daily for 8 consecutive days) and carbon tetrachloride are the drugs of choice.

DICROCOELIASIS, CLONORCHIASIS AND OPISTHORCIASIS

These diseases are all due to flukes that in man live in the intrahepatic bile ducts. They have a greater tendency than *Fasciola* to produce adenomatous hyperplasia of bile ducts. Clinically and pathologically, these conditions are very similar to fascioliasis. In all of them the diagnosis is based on finding the ova in the feces or in duodenal aspirations. No specific treatment is known for these 3 distomatoses.

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AMYLOIDOSIS OF THE LIVER

Maurice H. Stauffer, M.D., *and David C. Dahlin,* M.D.

ı 1853 Virchow used the term "amy- " for a substance present in many of the ıns that gave a starchlike staining reac- , although previous to that time the en- had been known as lardaceous disease. n the time generalized amyloidosis was recognized its association with various ilitating diseases has been noted, and atic involvement has been common, g mentioned in more than 60 per cent of cases.[6] The fact that the disease is quite and frequently has not been suspected r to necropsy seems to emphasize the culty of clinical diagnosis.

n spite of much study many aspects he disease remain obscure. Experimen- , amyloidosis has been produced in ous animals by the injection of toxins,[1] eria, casein[11] and other protein sub- ces. In some of the animals there has n an associated hyperglobulinemia which been suggested as the etiologic factor.[10] occasional observation of hyperglobulin- a associated with tuberculosis and the uency of amyloidosis in multiple mye- a might lend some support to this theory pathogenesis. These observations have to one of the hypotheses that amyloido- is a disease of obscure derangement of tein metabolism.

he chemical nature of the amyloid ma- al has not been identified completely but ally has been considered to be a complex tein combined with chondroitinsulfuric l,[16] although many qualitative differ- es have been noted. Amyloid is a homo- eous, amorphous eosinophilic material shows metachromatic staining with dyes n as methyl violet and methyl green. It ally has an affinity for Congo red and stains yellow or faintly pink by the van Gieson connective-tissue technic. The appearance of amyloid when stained with hematoxylin and eosin is ordinarily quite characteristic. A stain to show metachromasia may be desired for confirmation. The van Gieson technic differentiates amyloid from brilliantly red-staining hyalin or collagen in the occasional troublesome case.

CLASSIFICATION

Since the clinical and pathologic manifestations of amyloidosis are variable, several authors, such as Lubarsch,[20] Reimann and co-workers[25] and Dahlin,[7] have offered classifications of the different forms. Dahlin's classification is as follows:

1. Primary amyloidosis
    - A. Systemic
    - B. Focal or tumefactive
2. Amyloidosis complicating myeloma
    - A. Systemic
    - B. Focal or tumefactive
3. Secondary amyloidosis

PRIMARY AMYLOIDOSIS

Primary amyloidosis occurs in the absence of any predisposing disease. It is the rarest form of the disease—only 70 cases were reported in the literature up to 1950.[8] Other terms that have been used for this form are "paramyloidosis"[32] and "atypical amyloidosis."[20] It has a predilection for mesodermal structures, such as muscle, blood vessels and the heart. Widespread deposition of amyloid is the rule, and the cardiac involvement that occurs in most cases is the basis for the fact that myocardial failure is the commonest

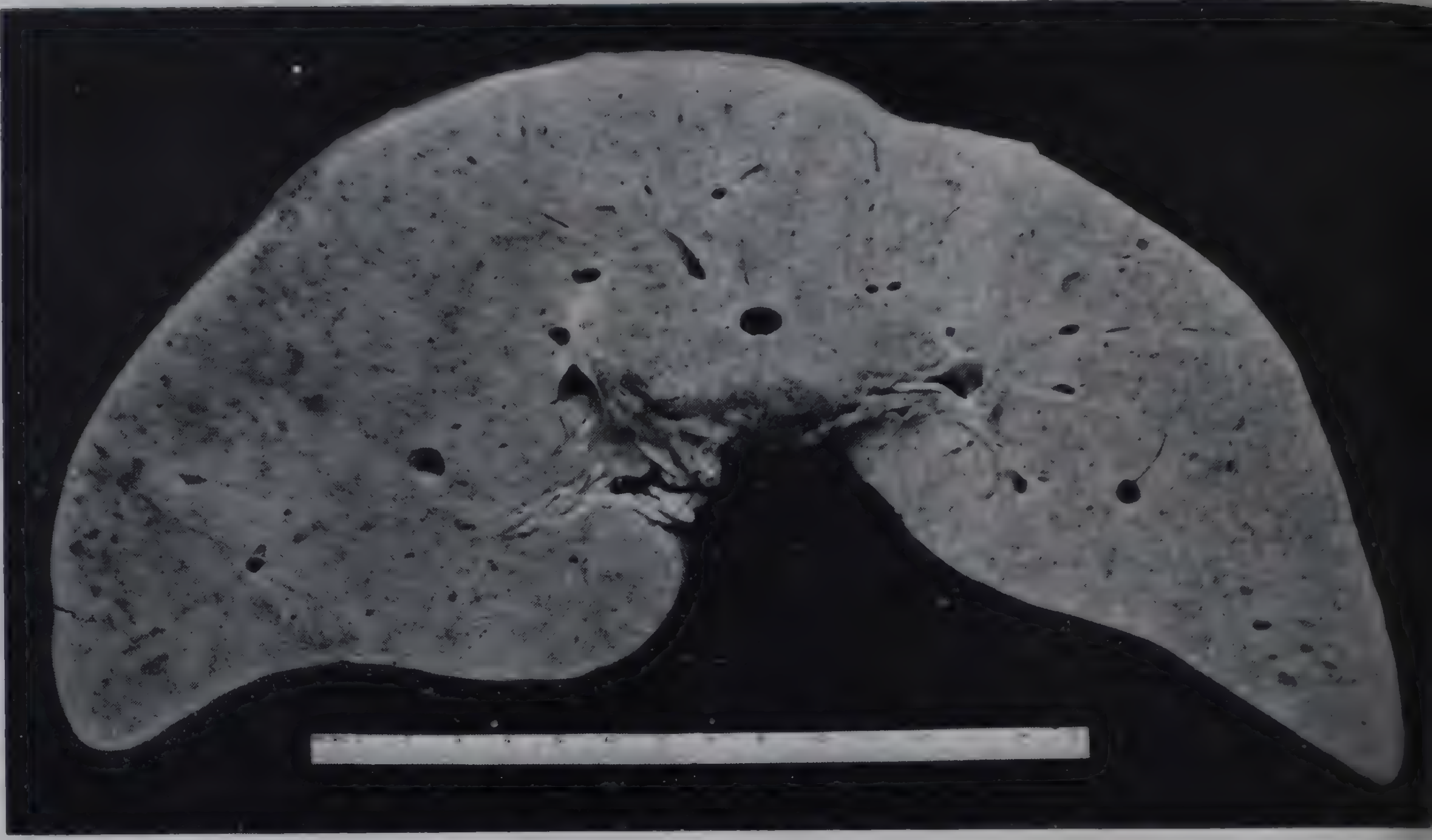

FIG. 215. A 4,000-Gm. liver with severe diffuse amyloidosis of the primary type. The predominant clinical signs had been related to hepatic involvement.

cause of death in primary amyloidosis. Macroglossia is a prominent feature in one third of the cases, and in more than one half there is amyloid in the mucosa or the muscle of the gastro-intestinal tract.[8] The spleen, the kidneys, the adrenal glands and the liver are infiltrated less commonly in primary amyloidosis.[6] Paradoxically, recent studies[38] have emphasized that hepatic involvement alone can be the prominent feature. In these cases the liver is firmer than normal; it may assume a somewhat translucent or brittle nature, owing to the waxy deposits (Fig. 215). Histologic study (Figs. 216, 217 and 218) reveals this substance on the reticular framework that separates the cords of hepatic cells from the sinusoids, and when this intralobular deposition becomes severe there is atrophy of the hepatic cells. The arteries and the veins of the portal triads usually have thickened walls and narrowed lumens owing to amyloid deposition in the media. Heavy infiltration in these vessels is more common in primary than in secondary amyloidosis and may be a helpful differential feature.

Renal deposits of amyloid ordinarily coexist in patients with hepatic involvement, resulting in albuminuria which can be severe The presence of amyloid in striated muscle joints, blood vessels, lungs and spleen ca

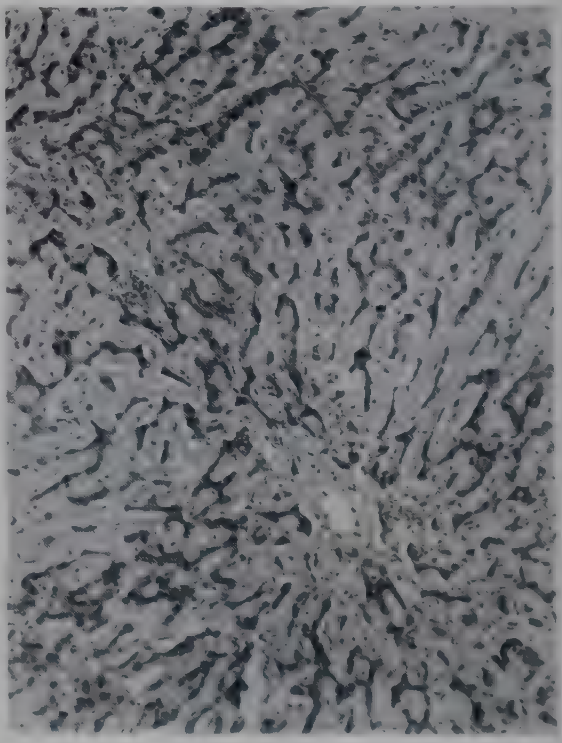

FIG. 216. Severe, diffuse, hepatic parenchymal amyloidosis of the primary type, histologically quite like the secondary variety (hematoxylin and eosin. × 85).

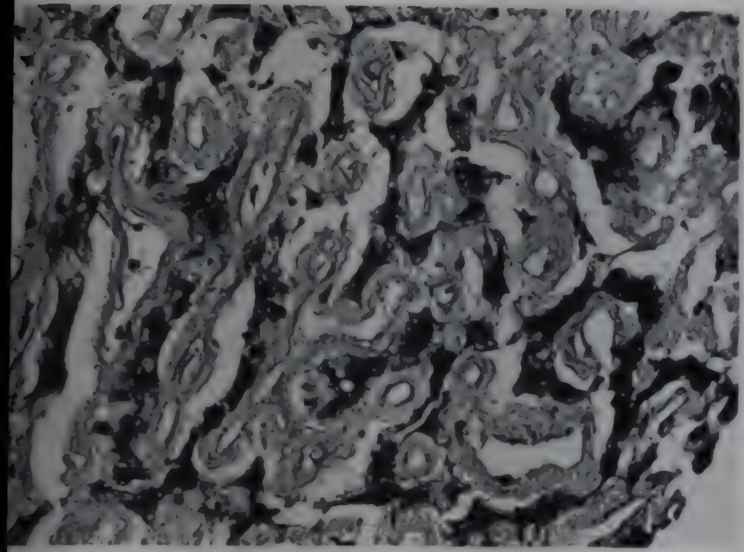

FIG. 217. Needle biopsy specimen with pale-staining amyloid between the sinusoids and the dark-staining hepatic cords. Detail of the hepatic cells has been altered by the special stain (Mallory's phosphotungstic acid hematoxylin. × 325).

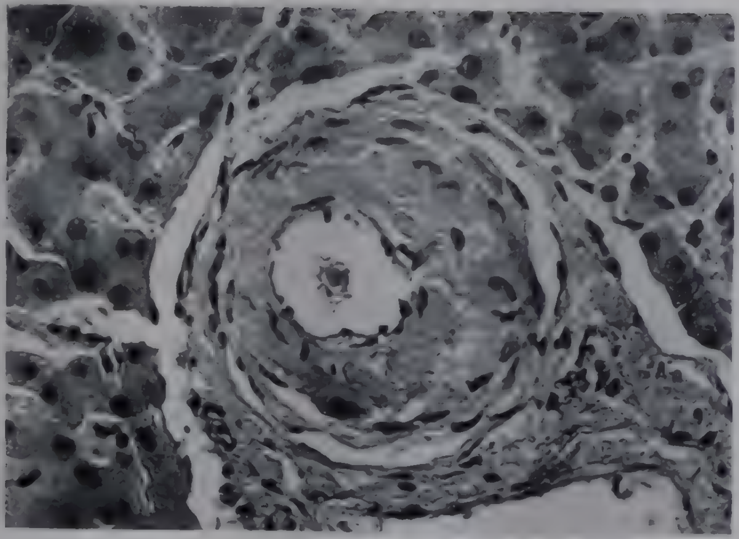

FIG. 218. Vessel of portal triad, showing prominent amyloid infiltration in a case of primary systemic amyloidosis (hematoxylin and eosin. × 400).

ccount for other symptoms. The disease is isually systemic, but focal masses may form ind these most often are seen in the urinary ind the respiratory tracts and in the skin. n some instances a single organ such as the ieart may be diffusely infiltrated. In primary myloidosis the substance is qualitatively lifferent from that in other forms of the lisease, showing little or no affinity for Congo red and less constancy in exhibiting netachromasia.

CLINICAL FEATURES

The bizarre clinical picture in primary myloidosis is responsible for the fact that he disease has been diagnosed correctly in nly a few cases prior to necropsy. Macrolossia is the one feature which most diectly suggests the disease, but this finding s absent in two thirds of the cases. A comination of macroglossia, albuminuria, skin esions, congestive heart failure and hepatonegaly is circumstantial evidence for prinary amyloidosis. Since more than 50 per ent of patients with the primary form die f cardiac causes, unexplained congestive ailure,[8] especially if associated with marked lbuminuria, should make one think of myloidosis as a possible cause. In other nstances the clinical picture has resembled nat of constrictive pericarditis[13, 22] with a high venous pressure, hepatomegaly and atypical cardiac findings.

Although hepatic infiltration is noted in only one third of the cases of primary amyloidosis,[8] recently it has been observed that hepatic signs and symptoms may dominate the clinical picture. In 1950 Wollaeger[38] found that 8 patients, making up approximately 10 per cent of the recorded cases, presented with predominantly hepatic findings. Since that time others have been reported, and we have observed additional cases. Jaundice has been reported exceedingly rarely in secondary amyloidosis, since only 2 cases[30] have been mentioned, but Stauffer[30] found reports on 6 patients[2, 5, 8, 21, 40] with jaundice in primary amyloidosis, which seems to be significant, since the latter form of the disease is much less common. Jaundice, hepatomegaly, ascites and edema are the reported findings indicative of hepatic involvement.[38] Most cases of this variety simulate cirrhosis of the liver[14] with hepatomegaly and ascites. The liver is usually hard, smooth and quite large, extending into the left upper quadrant. In 2 cases we have noted a hepatomalike enlargement on the surface of the liver near the costal margin, a feature that seems to be worthy of comment. The hepatic enlargement with ascites and debilitation of the patient may suggest metastatic carcinoma. Hepatomegaly with marked albuminuria should lead one to suspect amyloidosis, since albuminuria is not common in cirrhosis and metastatic carcinoma. Spider angiomas have been reported with primary amyloidosis, but esophageal varices have not been observed.

Since amyloid interferes with function of the liver only by pressure and atrophy of the hepatic cells, patients with hepatic signs and symptoms usually have pronounced hepatomegaly with severe infiltration. Petechiae and purpuric areas are noted frequently in primary amyloidosis but also are seen in cirrhosis, thereby not representing a helpful differential point. Because of these bleeding tendencies primary amyloidosis has been diagnosed erroneously as thrombocytopenic purpura.

Primary amyloidosis that involves the gastro-intestinal tract may cause hemorrhage or simulate gastric carcinoma or nontropical sprue. Infiltration of muscle and skin has led to a picture of "pseudoscleroderma" in some cases. Kernohan and Woltman[19] and others have reported a peripheral neuritis in primary amyloidosis, which can be a major or a minor aspect of the clinical picture. Stauffer and Dahlin[31] have observed 2 patients with postural hypotension as a prominent symptom.

AMYLOIDOSIS COMPLICATING MYELOMA

Although this form of amyloidosis might logically be considered a secondary one, ordinarily it is afforded a special place in the classification for 2 reasons: (1) the remarkably common occurrence of this complication of myeloma; (2) when there is a systemic distribution of amyloid in patients with myeloma, the severe deposition usually is found in the organs most involved in primary systemic amyloidosis.[3]

It has been estimated that between 5 and 10 per cent of patients with disseminated myeloma harbor deposits of amyloid. With or without a systemic distribution, these deposits may assume the local or tumefactive form. Such tumorous deposits of amyloid may appear in various organs, including bone, or may be present within the myelomatous masses themselves. Severe involvement of the liver with production of signs and symptoms of hepatic disease has been considered to be unusual, although minor involvement has been observed. In one case by needle biopsy of the liver, Stauffer found the hepatomegaly associated with myeloma to be due to amyloidosis. Som workers have cautioned that an underlyin myeloma should be ruled out in all patient with systemic amyloidosis thought to be o the primary type. Stauffer and Dahlin[31] hav observed a second case in which hepatomegaly due to amyloid was a finding fo 1 year prior to the establishment of th diagnosis of multiple myeloma.

SECONDARY AMYLOIDOSIS

This is the commonest form of the diseas and occurs as a complication of chronic diseases, such as tuberculosis, bronchiectasis osteomyelitis, syphilis, malignant tumors lymphosarcoma and rheumatoid arthritis. I some series, as high as 88 per cent of th cases of secondary amyloidosis have bee associated with tuberculosis.[24] In recent year the incidence of tuberculosis and chroni suppurative diseases has decreased, whic probably accounts for the fact that at th Mayo Clinic during the past 5 years rheumatoid arthritis has been the most commo inciting disease in secondary amyloidosis. The liver is one of the organs most frequently involved, this being noted in 60 t 87 per cent of cases in various reporte series.[6, 26] Hepatic infiltration usually is see in combination with involvement of th spleen, the kidneys and the adrenal glands– the organs most often attacked in secondar amyloidosis. Although involvement of th liver is frequent and may be severe, hepati failure is most unusual, since the underlyin disease is the cause of death in a majorit of the cases, with a small percentage of patients dying in uremia. Renal infiltration the most consistent feature of the secondar type.

Pathologically, the liver in secondar amyloidosis is grossly indistinguishable fro the liver in the primary form. It tends to firm and large—Pearlman[24] reported weigh of more than 4,000 Gm. in 9 cases. Micr scopically, the differentiation of prima from secondary amyloidosis of the liver ca not be made with certainty. Parenchym deposition in so-called Disse's space is ide l in both forms. The small vessels in portal triads are affected in most cases secondary amyloidosis and at times may the only location of hepatic amyloid, but involvement tends to be minimal com-ed with that of the primary form.

Clinical Features

Clinical manifestations of secondary yloidosis are not so variable as in the mary form and most commonly are re-ed to renal dysfunction. In many cases symptoms are obscure, but persistent uminuria in a patient with a chronic sup-rative or malignant disease is the leading e in secondary amyloidosis. It is safe to ume that patients without albuminuria do t have significant secondary deposition of yloid. In advanced cases hepatomegaly, enomegaly and edema or the full nephrotic drome are the features.

Although hepatomegaly occurs in 60 to per cent of the cases of secondary amyl-losis, jaundice and ascites of hepatic gin are rare. Spain and Riley,[29] and Tiber d co-workers[33] are the only authors re-rting jaundice associated with this disease. cause of a combination of hepatic and al involvement it is often impossible to termine the cause of the lowered values serum albumin leading to edema. Occa-nally, cases in which diarrhea has resulted m amyloid infiltration of the intestine ve been mentioned, but Addison's disease ulting from destruction of the adrenal nds in secondary amyloidosis is rare. In-lvement of mesodermal structures, such as od vessels and the heart, is absent or nimal so that cardiac insufficiency does t constitute a threat in secondary amyloi-sis.

LABORATORY FEATURES

In both primary and secondary amyloi-sis the laboratory data tend to be quite nilar but nonspecific for the disease. epatic dysfunction is shown best by use the sulfobromophthalein (bromsulpha-n) excretion test. Despite severe hepatic iltration, the degree of dye retention may minimal. In 2 cases in which the diag-sis was proved by needle biopsy the test indicated a 6 per cent retention at the end of 1 hour in each instance.[30] Clinical jaundice, which is more frequent in primary amyloidosis, is manifested by an increase of the direct-reacting fraction of the serum bilirubin. Although a lowered value for serum albumin has been called the most common laboratory abnormality,[33] this is not a constant feature, and the values for serum proteins may be extremely variable. Ordinarily, serum globulin is not increased, and even in amyloidosis associated with myeloma hyperglobulinemia is not a particular feature. Results of the thymol turbidity and cephalin-cholesterol flocculation tests usually have been normal. Increase of alkaline phosphatase has been reported. Of interest is the observation by Stauffer and Dahlin[31] that several patients have had increased concentrations of serum cholesterol and total lipids. In amyloidosis associated with myeloma, the latter diagnosis is established in the usual manner, on the basis of such findings as Bence Jones proteinuria and the typical characteristics of the sternal marrow.

DIAGNOSIS

Congo Red Test

Other than tissue biopsy, the Congo red test is the only method of diagnosis. This test is based on the fact that certain types of amyloid have an affinity for Congo red and thus remove measurable quantities from the blood. The test as originated by Bennhold[4] compared the amount of dye present after 60 minutes with a standard based on the amount noted 4 minutes after injection. Although originally a 60 per cent removal was considered to be diagnostic of amyloidosis, later reports showed that 90 to 100 per cent removal offered a much more nearly accurate basis for diagnosis. Paunz[9, 23] suggested a simpler method which avoided use of the standard: after injecting a smaller dose (1.2 mg. per kilogram of body weight) he read the result as positive if there was 100 per cent removal at the end of 1 hour, or negative if any dye was found in the blood. In our experience with the Paunz technic no false positives have been noted, although adequate data are lacking about false negatives. A positive result with the

Paunz test or 90 per cent removal of the dye with the quantitative Congo red test is nearly always indicative of amyloidosis.

One of the most important observations is that the test often gives a negative result in primary systemic amyloidosis because in this form of the disease the amyloid has little affinity for Congo red. Since there is usually considerable amyloid in the liver in patients with the secondary type of disease, and also in some patients with the primary form, absorption by this large organ may be chiefly responsible for a positive result with the Congo red test. In patients with skin lesions this test should not be used, because it can result in a permanent red discoloration of the cutaneous areas. Dermatologists have used a local injection to prove the affinity for Congo red in these cases.

BIOPSY

Since amyloid infiltrates many of the organs and tissues of the body, for a long time biopsy has been used to verify the diagnosis. This procedure is most important in cases in which the diagnosis is obscure and especially in primary amyloidosis or that form associated with multiple myeloma when the Congo red test may give negative results. Josefson[18] in 1916 employed needle biopsy of the spleen, but Waldenström[37] in 1928 first used needle biopsy of the liver to verify the presence of amyloid. Since secondary amyloidosis involves the liver diffusely and is present in two thirds of the cases, needle biopsy of the liver is being used currently to establish the diagnosis. Sherlock,[28] Volwiler and Jones,[36] Topp and coworkers,[34] Iversen and Roholm,[17] Stauffer,[30] and Wold[39] are among those reporting positive diagnoses from needle biopsy of this organ. Most interesting is the fact that the diagnosis can be made by this method in some cases of primary systemic amyloidosis in which the Congo red test gives negative results.[31] One death has been reported from hemorrhage subsequent to needle biopsy in amyloidosis;[36] however, Stauffer and Dahlin have established the diagnosis by this method in 11 cases without complication.[31] Occasionally, the diagnosis has been made by biopsy of the liver at laparotomy.

Selikoff and Robitzek[27] have found that gingival biopsy gives positive results in proved cases of secondary amyloido When macroglossia is present biopsy of tongue is performed easily. The skin, s ated muscle, mucous membranes, lyn nodes and the liver have all been reported sites of positive biopsy specimens in prim amyloidosis. We believe that needle bio of the liver may prove, paradoxically, to an important method of diagnosis for p mary amyloidosis, although deposits can missed if they are not widely distributed. cases in which cardiac involvement is as ciated with an elevated venous pressure. tempts should be made to lower the press by the use of digitalis and diuretics prior hepatic biopsy. The unwary pathologist n miss extensive deposits in sections of aspirated specimen unless he is alerted to possible presence. The material is clos coapted to the cords of hepatic cells and be difficult to visualize without special sta the most helpful of which are methyl vi and methyl green.

PROGNOSIS AND TREATMENT

Numerous substances have been used treat primary amyloidosis but thus far have been fruitless.[12] In our experience mary amyloidosis is fatal within a year, though cases in which the patients li longer have been reported. Gross[15] fou cortisone to be of no value in the treatm of 2 patients. In amyloidosis associated w myeloma the underlying disease ordina governs the patient's progress, but occasio patients die of the complicating amyloid even before the myeloma becomes clinic evident.

In secondary amyloidosis the outlook variable. In several cases regression or appearance of the disease has been repor after successful treatment of the associa disease. In 1928 Waldenström[37] showed aspiration biopsy that amyloid had dis peared completely from the liver in 3 tients after proper surgical treatment tuberculous lesions. A few spontane "cures" have been reported.[35] In some ca the amyloid status may remain unchan for several years. It should be conside that amyloidosis is not a contraindicatio treatment of the primary disease, whether surgical or other means.

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DISEASES OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

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INTRODUCTION

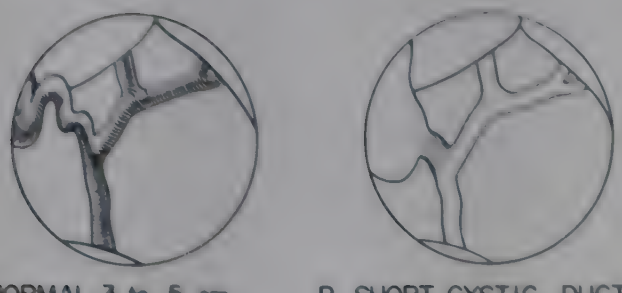
problems associated with the treat-
of biliary tract disease are among the
common encountered by the clinician.
ubt, in the future, complaints involv-
e biliary system and requiring opera-
tervention will be even more frequent.
al statistics show a definite increase in
an of life,[34] and it is in the elderly that
idence of gallstones reaches its peak.[37]
rmore, unfavorable consequences of
thiasis, such as acute cholecystitis and
on duct stone, also increase with each
e of life. Early cholecystectomy for
tomatic gallstones might well be con-
d in the over-all plan of management
ler to avoid the later occurrence of
serious complications in the older
risk" patient. However, a number of
ians, in spite of the steadily improving
dity and mortality rates in biliary sur-
are hesitant to advise operative inter-
n, except in the presence of complica-
This attitude has been fostered in the
by reports of unsatisfactory results.
gh of these "symptomatic and opera-
failures have occurred in the past to
nce both patients and physicians.[33]
se uniformly good results can be ob-
from biliary surgery, every physician
d review from time to time all aspects
own management of gallbladder dis-
Improved results may be anticipated if
mptoms of the patients selected for sur-
rise from proved biliary tract disease, and if the operation, regardless of indication, is thorough and complete.

SURGICAL ANATOMY AND ANOMALIES

Complete familiarity with the surgical anatomy and high incidence of congenital anomalies of the biliary tract is essential in the diagnosis and the treatment of the biliary tract. This familiarity is of particular importance in the area of the junction of the cystic and the hepatic ducts. Coller has pointed out that there are more important anatomic variations in this small area, the size of a half dollar, than anywhere else in the body. This suggests that the use of the term "anomalies" should be limited to those abnormalities which manifest themselves in early childhood. Many of the variations persist throughout life without symptoms, while others predispose to inflammation or prove to be troublesome in the presence of stones. Of more importance, all too many of these abnormalities are unrecognized by the unwary surgeon at the time of operation, resulting in injuries to the ductal system or incomplete surgery with serious sequelae. It follows that the surgeon who proposes cholecystectomy must be thoroughly familiar with and qualified to recognize and cope with these anatomic variations.

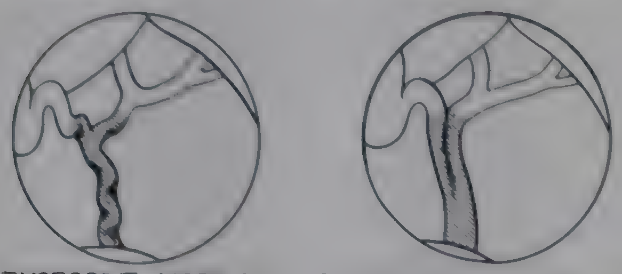
EMBRYOLOGY

The gallbladder, the bile ducts and the secretory tubules of the liver arise as a



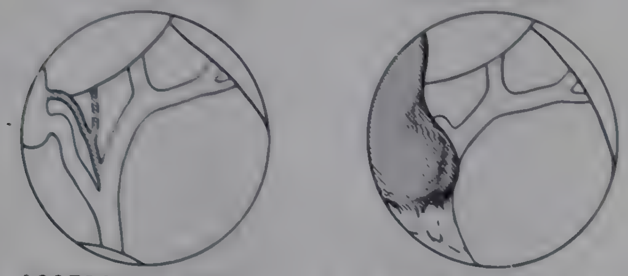
A. NORMAL 3 to 5 cm

B. SHORT CYSTIC DUCT



C. EXCESSIVE MOBILITY OF COMMON DUCT

D. CYSTIC PARALLEL WITH COMMON DUCT



E. ACCESSORY CYSTIC OR HEPATIC DUCT

F. LARGE PENDULOUS AMPULLA

FIG. 219. Variations of gallbladder and extrahepatic bile ducts. (A) The length and the insertion of the cystic duct vary considerably, but on the average it is 3 cm. long and descends to join the lateral aspect of the common hepatic duct approximately 1 inch below the junction of the right and the left hepatic ducts. Possible anomalies include variations shown in B to F. (B) A short but wide cystic duct which predisposes to trauma. (C) If excessive mobility of the common duct is present, traction on the gallbladder may tent the ductal system and may result in accidental injury. (D) The cystic duct descends for varying distances parallel with the common hepatic duct in nearly 1 out of every 4 patients. (E) Accessory cystic ducts may join the hepatic, the common hepatic, the main cystic or the common bile ducts. (F) When the ampulla is large and pendulous or the site of an impacted stone, it may obscure the bile ducts and the hepatic arteries.

diverticulum from the ventral wall of the foregut during the fourth week of embryonic life. This hepatic diverticulum elongates and divides to form multiple hepatic ducts and columns of secretory cells. A secondary outgrowth develops from the distal portion of this diverticulum to form the gallbladder and the cystic duct. The common bile duct then becomes the tubular portion, extending from the junction of the cystic and the common hepatic ducts to the duodenum. Early in development, the lumen of the entire ductal system becomes occluded by cellular hyperplasia and later recanalizes. Failure of this process produces varying degrees of congenital atresia of the common or hepatic ducts. The vascular, the lymphatic and the nerve supplies to the biliary tract system have the same origin as the portion of the foregut that develops into pancreas, the duodenum, the sphincter of Oddi, the pylorus and the liver, and this may account for the similarity of signs and symptoms in diseases of this part of the digestive tract.

GALLBLADDER

Normal Anatomy. The normal gallbladder is a thin-walled, pear-shaped reservoir with a capacity of some 30 to 60 cc., lying in a fossa on the inferior surface of the liv which separates the right lobe from th quadrate lobe. Its bulbous extremity fundus occupies the cystic notch in the liv margin and may come in contact with th anterior parietal peritoneum behind the nin costal cartilage in the angle between th right rectus muscle and the costal margi The gallbladder runs upward to the left ar posteriorly in the cystic fossa; it is continu inferiorly into the tapering neck of the ga bladder, which curves medially in the for of an italic letter *S* and terminates in th cystic duct. The ampulla, or Hartmann pouch, is the dependent saccular portion the gallbladder which bulges forward b tween the body and the cystic duct into th uppermost free portion of the lesser ome tum. When large and pendulous or the si of an impacted stone, it may obscure th bile ducts and the hepatic arteries (Fi 219). In these instances, failure to mobili the ampulla may result in operative inju to the ductal system.

Anatomic Relations. The gallbladder attached to the liver by loose connecti tissue and peritoneum reflected from its sid Small vessels which run from its upper w into the liver may be the source of troubl

bleeding which makes closure of the
bed advisable. The escape of bile from
r small biliary channels (hepatocystic
) makes insertion of a drain following
cystectomy advisable. Coller has sug-
searching for and catheterizing an
ged hepatocystic duct as a means of
ing access to the intrahepatic biliary
nels when dealing with atresia or non-
ble benign strictures of the biliary
The anatomic relation of the gall-
er to the duodenum and the colon is
that adherence is not infrequent and
onally leads to perforation into the
l.

ariations. Major variations of the gall-
der seldom occur.[26] Occasionally, the
ladder is suspended by a mesentery, or
ay be deeply buried in the liver sub-
e, making exposure difficult. Complete
artial duplication, cystic compartmen-
tion and constrictions of the body have
reported. Congenital or adhesive fixa-
of the gallbladder fundus produces
ng between the body and the fundus
the cholecystographic appearance of
allbladder called the Phrygian cap. This
no clinical significance.

CYSTIC DUCT

ormal Anatomy. The length and the in-
on of the cystic duct vary considerably,
on the average it is 3 cm. long and
ends to join the lateral aspect of the
non hepatic duct approximately 2.5 cm.
the junction of the hepatic ducts. The
n of the cystic duct is compromised by
l mucosal folds (Heister's valves) which
impede the passage of small stones out
e gallbladder and make catheterization
e passage of instruments into the com-
duct via the cystic duct difficult.

ariations. Possible anomalies include a
t but wide cystic duct which predisposes
auma or inadvertent ligation of the com-
bile duct (Fig. 219). The cystic duct
ends for varying distances parallel to
common hepatic duct in nearly 1 out of
4 patients and on occasion empties
tly into the duodenum. Failure to rec-
ze this important anomaly accounts for
mber of retained long cystic duct stumps,
h may be the basis for recurrent symptoms following cholecystectomy. If a cystic duct stump is mistaken for the common duct, and exploration is attempted, the surgeon finds it impossible to pass proximally into the hepatic ducts. In the presence of jaundice, a nonexistent obstruction of the common hepatic duct may be postulated and operative injury may result. Under these circumstances, caution must be exercised to avoid injury to the underlying ductal system. Accessory cystic ducts may join the hepatic, the common hepatic, the main cystic or the common bile ducts, while accessory hepatic ducts can empty into any of these sites or directly into the gallbladder. If the cystic duct is divided and overlooked, a temporary biliary fistula may result, or, more important, bile peritonitis or subhepatic abscess formation may occur.

COMMON BILE DUCT

Normal Anatomy. The common bile duct measures from 9 to 11 cm. in length and begins at the junction of the cystic and the common hepatic ducts. The upper third, or supraduodenal portion, is most accessible to the surgeon and descends along the right free border of the lesser omentum with the portal vein and the foramen of Winslow below and the hepatic and the gastroduodenal arteries on its left. Its color and a rather constant vein seen on its anteromedial wall are of value in identifying the bile duct. The middle third (retroduodenal) passes behind the first portion of the duodenum anterior to the vena cava and to the right of the portal vein approximately 2 cm. from the pylorus. Mobilization of the duodenum (Kocher maneuver)[3] provides access to this segment as well as the lower third (pancreatic) which lies behind or passes through the head of the pancreas and curves anteriorly before terminating in the posteromedial aspect of the second portion of the duodenum at about its middle. The intraduodenal portion passes obliquely through the duodenal wall and is joined by the pancreatic duct. The short common reservoir, which is the ampulla of Vater, narrows considerably before opening into the duodenal papilla and may prevent passage of small stones.

Anomalies of the common duct include congenital atresia or stenosis. This is the

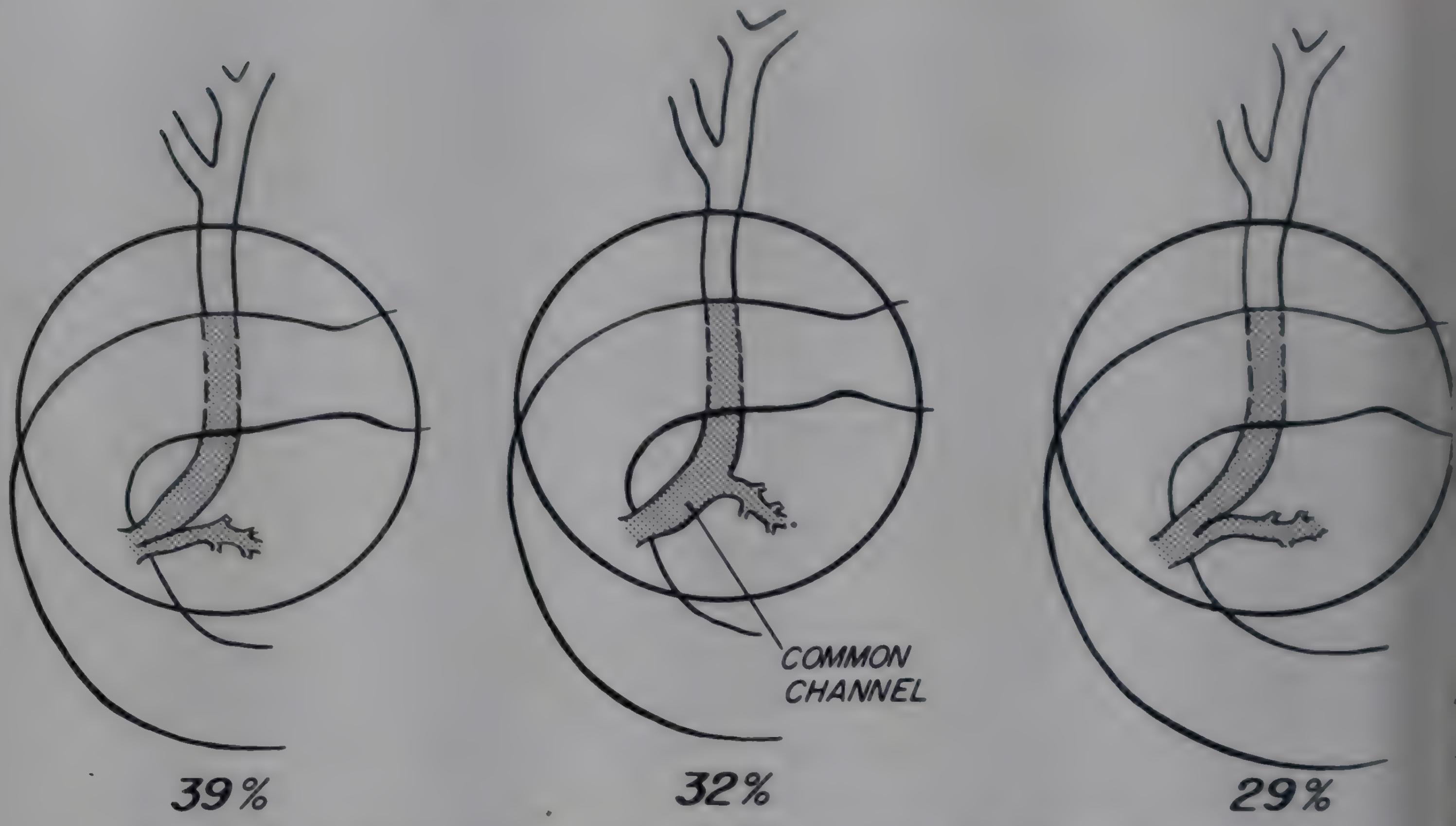


FIG. 220. Variations in the union of the pancreatic and the common bile ducts. (*Left*) Termination on duodenal papilla. (*Center*) Nearly 1 out of 3, or 32 per cent, join proximal to the ampulla of Vater, leading to a "common channel" for pancreatic and biliary secretions. (*Right*) Termination within the ampulla of Vater is the least common (29%).

most common cause of prolonged neonatal jaundice. Reduplications and saccular dilatations occur only in rare instances. Excessive mobility of the supraduodenal portion is a most important variation. This may allow traction on the gallbladder to tent the ductal system which may lead to accidental injury to the common bile duct. There is considerable variation in the union of the pancreatic and the common bile ducts.[32] Termination within the ampulla of Vater is least common (29%) (Fig. 220). In the presence of an impacted ampullary stone, blockage of pancreatic and common ducts prevents pancreatic as well as biliary secretions from entering the duodenum. Nearly 1 out of 3 join proximal to the ampulla of Vater, forming a "common channel" for pancreatic and biliary secretions. Impaction of a stone in the ampulla, spasm or fibrosis of the sphincter of Oddi may cause the reflux of bile into the pancreatic duct with subsequent pancreatitis.[20] This is the basis for removal of gallstones and/or sphincterotomy in some patients with chronic recurren pancreatitis.

SPHINCTER OF ODDI

The 4 intrinsic muscles of the sphincte of Oddi consist of 2 longitudinal muscl bundles which shorten the common duc and erect the papilla and 2 annular sheath around the common duct above and belov the point of entrance of the pancreatic duct. The duodenal musculature may act as a supplement to the control of bile drainag because contraction of the duodenum ob structs the intramural portion of the com mon duct and aids storage of bile.

Very little bile reaches the duodenun during the fasting state because increase tonus of the sphincter of Oddi diverts live bile into the gallbladder when common duc pressure exceeds the 50 mm. of water neces sary to force fluid through Heister's valves Spasm of the sphincter of Oddi may increase common bile duct pressure to 600 to 80 mm. water before bile flows into the duode

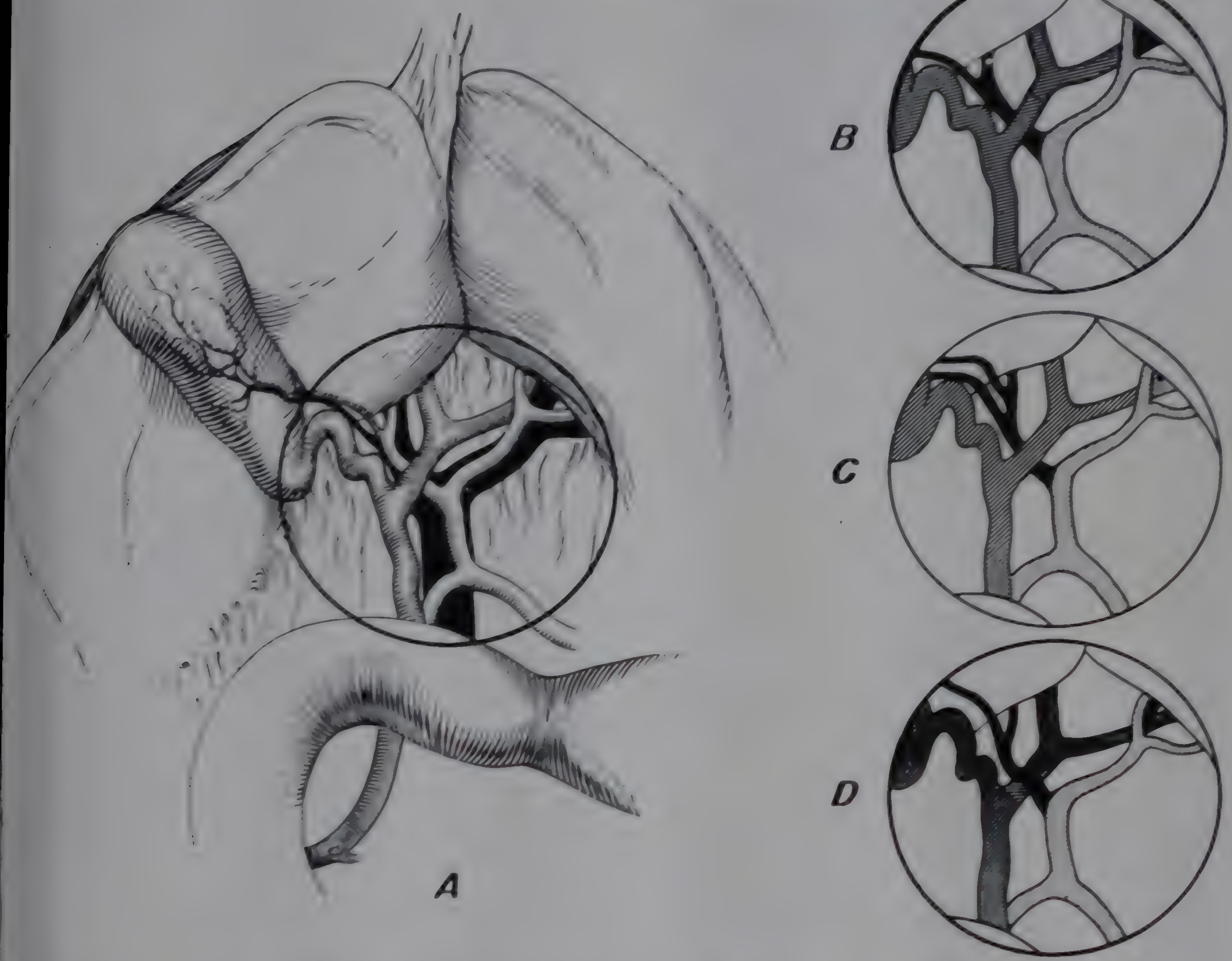


FIG. 221. (A) Normal anatomic relations of the gallbladder and the extrahepatic bile ducts. (B) The right hepatic branch lies parallel with and in close proximity to the cystic duct itself in nearly 1 out of every 5 patients. (C) Vessels corresponding to the anterior and the posterior branches of the cystic artery originate as separate vessels from the right hepatic artery in 15 per cent of patients. (D) The right hepatic artery passes in front of the common hepatic duct in some 12 per cent of cases.

m. This pressure will stop secretion of er bile, prevent contraction of the gall-dder and produce pain from ductal dis-tion.

ARTERIES OF EXTRAHEPATIC BILE PASSAGES

The arterial blood supply of the extra-patic bile passages is derived from the mmon hepatic trunk of the celiac axis ich divides behind the pylorus into the stroduodenal artery and the ascending patic artery proper (Fig. 221). Two small anches, the supraduodenal and the retroduodenal arteries, arise from the gastroduodenal artery and supply the respective portions of the duodenum and the common bile duct. An additional vessel, the posterior superior pancreaticoduodenal artery, turns posteriorly over the superior border of the pancreas and invariably passes across the anterior surface of the common bile duct.

Hepatic Artery. The hepatic artery proper ascends in the hepatoduodenal ligament toward the porta hepatis where, at varying distances from the liver substance, it terminates by branching into the right and the left hepatic arteries. During its course it lies medial to the common bile duct and anterior to the portal vein. These relationships are of considerable importance, inasmuch as vigorous bleeding from the cystic or the hepatic arteries may be controlled by compressing the hepatic artery between the thumb and the index finger as it courses upward in the gastrohepatic ligament. In turn, accurate visualization of the bleeding point permits ligation without fear of injury to the ductal system. In most instances (88%), the right hepatic branch passes behind the common hepatic duct (Fig. 221) and behind the cystic duct to the right end of the porta hepatis. It should be remembered, however, that the right hepatic branch lies parallel to and in close proximity to the cystic duct itself in nearly 1 out of every 5 patients and passes in front of the common hepatic duct in some 12 per cent of cases. With this in mind, the surgeon must take the precaution of ligating no artery until it is proved that the vessel enters the gallbladder so as to avoid mistaking an anomalous right hepatic or main hepatic artery for the cystic artery. Death may occur following ligation of the right hepatic artery.

Cystic Artery. The cystic artery runs downward and forward along the cystic duct to the gallbladder, where it divides into anterior and posterior branches. The anterior passes downward between the gallbladder and the visceral surface of the liver, giving off branches to both. Severance of these branches frequently gives rise to minor bleeding during a retrograde cholecystectomy, and they may require ligation. The posterior branch is distributed on the posterior surface of the gallbladder and lies between it and the peritoneum. Vessels corresponding to the anterior and the posterior branches of the cystic artery originate as separate vessels from the right hepatic artery in 15 per cent of patients. The unwary surgeon, having ligated one of these as the cystic artery, is suddenly faced with serious hemorrhage when the second vessel is divided. Common duct injury not infrequently occurs during blind clamping in an effort to control this brisk bleeding.

Veins of Extrahepatic Bile Passages

Venous blood from the gallbladder may pass directly into the liver by way of veins on its left side or may anastomose with small branches along the common duct coming from the intestinal tract and, in either case, on entering the hepatic parenchyma is soon confluent with the hepatic capillaries.[23] In neither case are there direct connections between the venous channels of the gallbladder and the portal system.

Lymphatic Drainage

Lymphatic drainage in general follows the arterial supply, but more specifically the lymphatic channels drain to 3 constant lymph nodes, i.e., one at the neck of the gallbladder, another at the junction of the cystic and the hepatic ducts, and the third near the termination of the common duct.[2] These may become enlarged in infections of the biliary tree or malignancy of the gastrointestinal tract, and have been mistaken for impacted stones. Metastatic involvement of such nodes must be considered in the differential diagnosis of obstructive jaundice. Small lymphatic channels traversing the liver bed are also of importance, since pathologic processes involving the gallbladder may spread early to the neighboring liver. Therefore, biopsies of adjacent liver areas are not representative histologically of the liver as a whole and should be taken as far removed from the gallbladder as feasible. The early inoperability of gallbladder carcinoma may be related to these lymphatic connections.

CHRONIC CHOLECYSTITIS AND CHOLELITHIASIS

Incidence of Gallstones

It has been estimated that gallstones are present in approximately 12 per cent of the adult population. Although rarely seen before age 20, the frequency of their occurrence and the number of complications resulting from their presence increase thereafter with each decade of life.[87] The highest incidence is among women 50 to 60 years of age and there is a sex-incidence of greater than 2 to 1 in favor of females.

The incidence of gallstones is higher in patients with hemolytic anemia (43%), diabetes (30.2%), portal cirrhosis, and duo-

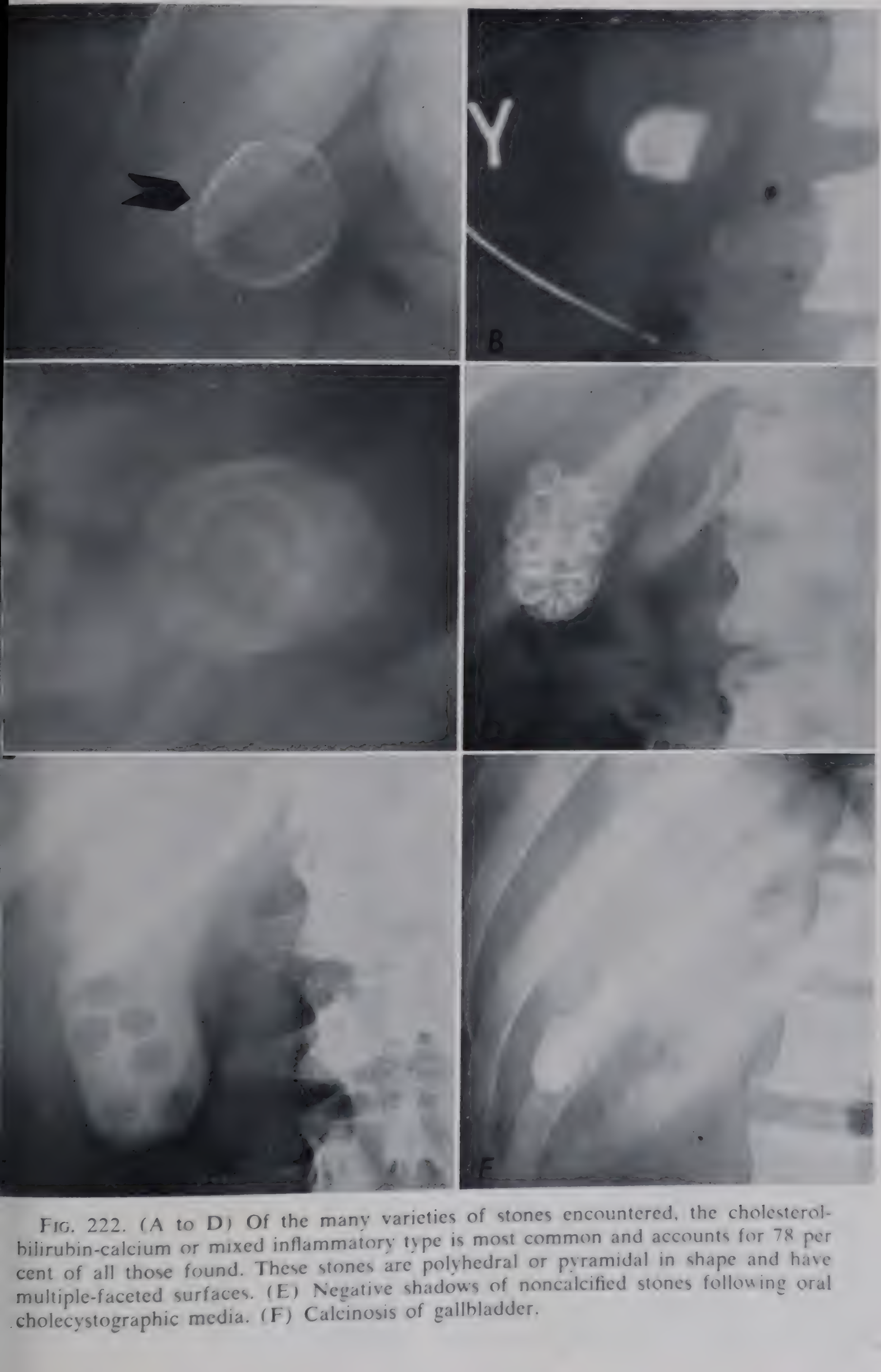


FIG. 222. (A to D) Of the many varieties of stones encountered, the cholesterol-bilirubin-calcium or mixed inflammatory type is most common and accounts for 78 per cent of all those found. These stones are polyhedral or pyramidal in shape and have multiple-faceted surfaces. (E) Negative shadows of noncalcified stones following oral cholecystographic media. (F) Calcinosis of gallbladder.

denal or gastric ulcer. Stones and biliary tract disease are found in one fourth of all females and one third of all males with acute pancreatitis. Oddly enough, there is a decreased incidence of gallstones in patients with pernicious anemia and tuberculosis.

PATHOGENESIS OF GALLSTONES

Factors which have been implicated in the pathogenesis of gallstones include biliary stasis, chemical irritation from retained bile, secondary bacterial inflammation, and disturbance of cholesterol metabolism. The old standbys of pregnancy, typhoid fever and obesity as etiologic factors are not as significant as was formerly believed.

VARIETIES OF GALLSTONES

Of the many varieties of stones encountered, the cholesterol-bilirubin-calcium or mixed inflammatory type is most common and accounts for 78 per cent of all those found. These stones are polyhedral or pyramidal in shape and, with multiple-faceted surfaces, vary in color from white or yellow to green, brown or black. Although the mixed inflammatory stones are usually one size, two or three generations may coexist. Pigment or bilirubin-calcium stones are less common (10.5%) and, being metabolic in origin, may form in the gallbladder or the extrahepatic bile ducts. These calculi are dark brown to black in color, are usually multiple and inasmuch as they appear to be a number of small stones welded together, they are commonly referred to as "mulberry stones." Pure cholesterol stones (10%), which are usually single, are also metabolic in origin, and since they are composed entirely of cholesterol, they are light in color and translucent. Calcium carbonate stones (1.5%) are rare and form when there is a low-grade chronic biliary obstruction. Absorption of bile and precipitation of calcium carbonate as soft stones, paste or liquid, which is commonly known as "milk of calcium bile," then occurs. Combination or compound stones have a mixed or inflammatory calculus at the center with other materials precipitated on the surface. The size of the gallstones as well as the amount of calcium or cholesterol present determines whether or not they will be visualized by x-ray examination. It should be realized,
however, that only a minority of gallst
can be demonstrated on the abdominal s
film, and a negative finding is of little
nificance in excluding their presence. Ch
and prolonged inflammation of the
bladder wall may result in its calcific
or the formation of many small stone
that on x-ray examination the gallbla
appears to be completely calcified (calc
sis of the gallbladder) (Fig. 222).
matter of fact, in the absence of a pre
nary scout film of the abdomen, it ma
mistaken for a normally visualizing
bladder following ingestion of a radiop
dye capable of concentration in the
bladder.

CHOLESTEROLOSIS AND HYDROPS ("STRAWBERRY GALLBLADDER")

Cholesterolosis, or a "strawberry
bladder," is a metabolic disease characte
by polypoid enlargement of the villi w
contain yellowish deposits of choles
which are visible grossly. Seedlike pr
tions from the mucosa may break off,
free in the gallbladder and act as a ce
nidus for crystallization of bile pigm
cholesterol or calcium. The lesion is of
clinical importance, and cholecystecto
not indicated unless stones are presen
hydrops of the gallbladder is produce
chronic obstruction of the cystic duct i
absence of acute inflammation. The pig
is absorbed from the contained bile, an
gallbladder distends because of cont
mucous secretion from its lining and
be palpable as a smooth tender mass
contents of the obstructed viscus are s
and are known as "white bile." Howev
the contents become infected, an emp
results, and operative intervention bec
urgent.

LOCATION OF GALLSTONES

Gallstones may be found anywhere
biliary tract but more commonly in the
bladder, the cystic or the common bile
Autopsy studies have shown that ov
per cent of patients with gallstones hav
or more calculi in the common bile du
equal importance to the surgeon is the
that stones are harbored in the main
hepatic ducts in some 7 per cent of
with cholelithiasis.[20]

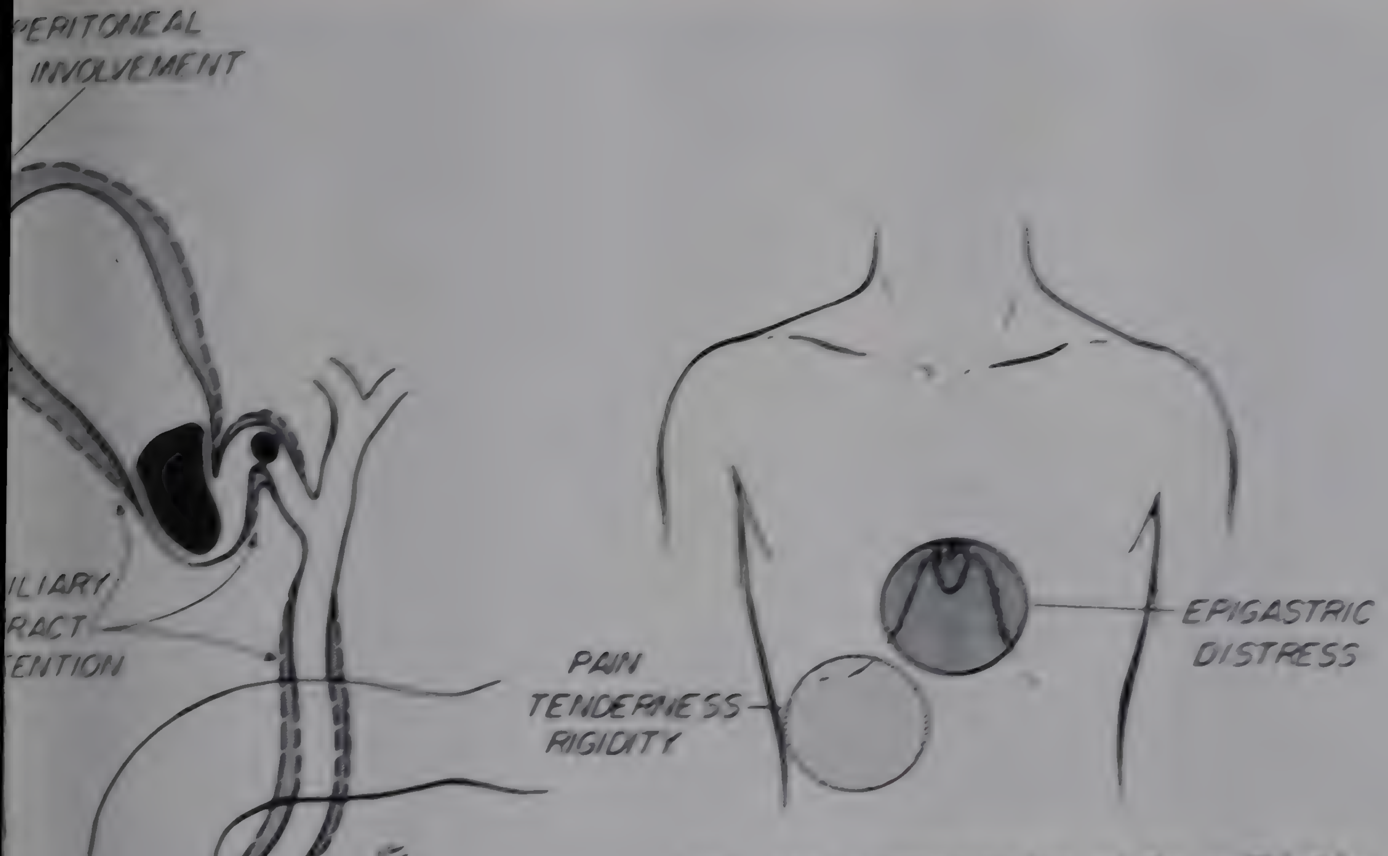


FIG. 223. Overdistention of the gallbladder produces a feeling of indigestion or deep epigastric discomfort. There is an absence of pain in the gallbladder area, unless the overlying parietal peritoneum is involved. Distention of the cystic and the common ducts produces the epigastric pain so characteristic of biliary colic and invariably is accompanied by nausea and involuntary vomiting.

MPTOMATOLOGY OF CHRONIC CHOLECYSTITIS

symptomatology of chronic chole-
with or without nonobstructing cal-
in the gallbladder, includes fullness
stric distress after eating, belching,
with occasional attacks of vomiting
most instances, an intolerance to
coarse foods.

minal pain, or "biliary colic," stands
he single most important complaint
ts with gallbladder disease. Although
cholecystitis may be complicated by
the absence of stones, it is extremely
d most likely results from temporary
ion or the passage of a mucous plug
the cystic duct. In general, the symp-
these patients without demonstrable
are so nonspecific that cholecystec-
seldom advisable.

stric discomfort, or "indigestion," is
tly described by patients with uncomplicated gallstones. The pain of biliary colic is also located in the mid-epigastrium; however, it is severe and incapacitating and accompanies mechanical obstruction of the cystic or the common duct. Gallstone colic begins abruptly; although the duration of the attack is relatively brief, frequently narcotics are required. Although there is no general agreement as to the exact mechanism by which epigastric pain is produced, it most likely results from distention of the biliary tree.

Experimental observation following mechanical distention of the gallbladder or the common duct by means of a balloon introduced at the time of laparotomy supports this explanation.[44] Overdistention of the gallbladder produced the feeling of indigestion or deep epigastric discomfort so common to patients with gallbladder disease (Fig. 223), but nausea and vomiting and referred pain to the back did not occur. Furthermore, there was an absence of pain in the gallbladder area unless the overlying parietal peritoneum was stimulated. This fits in with the clinical observation that some patients with an inflamed gallbladder have only mild symptoms referable to the right upper quadrant, and in these instances the peritoneum has not been involved.

Distention of the cystic and the common ducts produced the epigastric pain so characteristic of biliary colic and invariably was accompanied by nausea and involuntary vomiting, but again pain was not referred to the back or the right upper quadrant. The chief differences, both clinically and experimentally, between distention of the gallbladder and of the cystic and the common ducts is the severity of the pain and the occurrence of nausea and vomiting with the latter. Therefore, an accurate history may be sufficient to indicate the probable site of the offending calculus.

Inspiratory distress and splinting of the diaphragm were noted following distention of either viscus and are consistent with the clinical observation that the patients complain of shortness of breath during a gallbladder attack. Herein lies another reason for the not infrequent confusion of biliary colic with heart disease.

Although the majority of patients complain of right upper quadrant and epigastric pain, a few describe pain projection to the left upper quadrant, to the back, beneath the tip of the scapula and to the right shoulder. The mechanism of referred pain in these instances has not been explained satisfactorily.

PHYSICAL EXAMINATION

Physical examination in patients with chronic cholecystitis and cholelithiasis may be disappointing. Pain on deep inspiration while exerting pressure under the right costal margin (Murphy's sign) or slight tenderness to deep palpation in the right upper quadrant may be the only positive findings, and these too may be absent even when the patient only recently has recovered from an attack of biliary colic. The diagnosis of a hydrops of the gallbladder and a stone impacted in the cystic duct should be considered if a rounded globular mass is palpated in the right upper quadrant.

X-RAY EXAMINATION

A plain film of the abdomen demonstra
calculi in 5 to 20 per cent of all cases w
cholelithiasis and, if not taken before cho
cystography, milk of calcium bile, radiopaq
stones of certain densities, or diffuse calc
cation of the gallbladder wall may be o
scured by contrast material and overlook
For this reason an abdominal scout film b
fore the administration of contrast media
preferred, and if no abnormalities are se
cholecystography is indicated.

A number of oral cholecystographic me
are now available for selection, and no dou
many more will be developed in the futu
Each preparation has certain characteristi
and the choice of media depends upon t
problems presented by the individual patie

When using the newer cholecystograp
media, the density of a normally visualiz
gallbladder may be so intense that it obscu
the presence of nonradiopaque gallston
To obviate this difficulty, the position of t
patient should be varied from the erect
recumbent attitude using anteroposter
lateral and oblique views of the right upp
abdomen to obtain the layering effect as w
as different tissue densities. The right late
decubitus position employing horizon
x-ray beams is particularly useful in dete
ing the layering of stones in the top, the b
tom or between the layers of bile or contr
media. Anteroposterior compression fl
the gas shadows upward and to the l
whereas the liver and the gallbladder co
to lie in a comparatively free space in t
right lower quadrant.

Although emptying studies after a fa
meal are of no value in determining functi
because there is less dye in the gallbladd
they may show contraction of the gallblad
around stones not shown previously. On o
casion the taking of either the fatty meal
saline for its chologogue action will caus
faint shadow to be developed in the hep
or the gallbladder area or will concentr
and empty a gallbladder too faint to be s
previously. Nonvisualization of the g
bladder in the absence of demonstrable c
cified stones indicates the need for
examination with an equivalent or dou
dose of contrast material.

A variety of intravenous contrast me

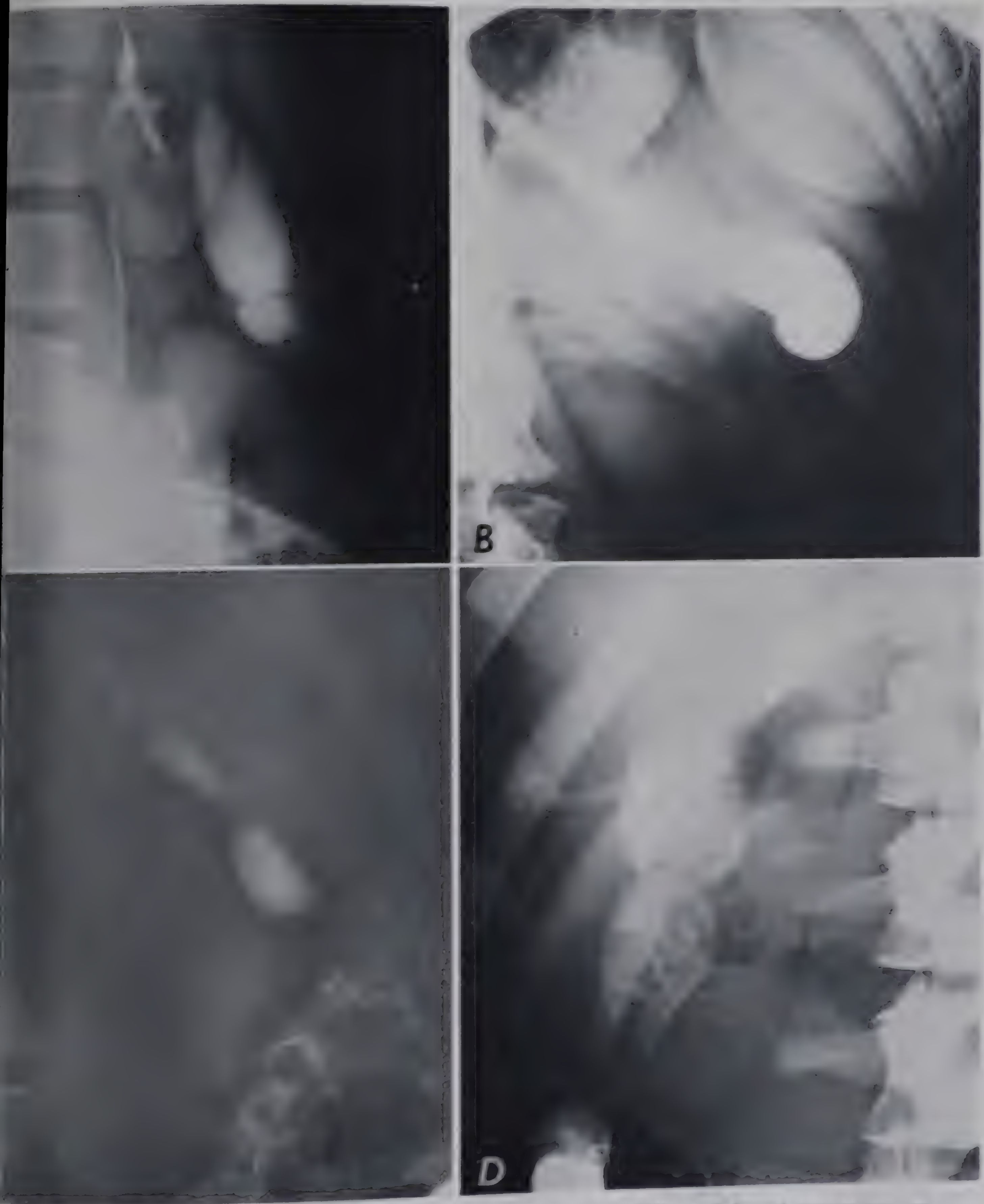


Fig. 224. Too much emphasis has been placed on poor filling, delayed emptying, or an unusual size or shape of the gallbladder as shown by cholecystogram. (A and B) Phrygian cap. (C) Segmentation of gallbladder. (D) Segmentation with nonradiopaque gallstones.

are being investigated, and the clinical experience with one of these has been reported recently by Glenn.[24] The availability of such media may make possible study of both normal and pathologic physiology of the ductal system and may throw new light on the so-called biliary dyskinesia.

SELECTION OF PATIENTS FOR OPERATION

Cholecystography. Because the diagnosis of gallbladder disease is confirmed so easily by means of a cholecystogram, this method of examination should be utilized routinely for guidance in the selection of patients for operation. The best results follow surgery in the patient who has had gallbladder colic and in whom gallstones are demonstrated by cholecystogram.

The indications are defined less clearly in a large group of patients in whom the gallbladder does not fill by cholecystogram and no stones are visualized. Surgery is not recommended in this group unless there has been a history of typical gallstone colic severe enough to require narcotics. Even under these circumstances, a repeated cholecystogram with reinforcement of the dye is very desirable.

One of the pitfalls in the selection of patients results from the acceptance of a nonfilling gallbladder on one test as an absolute indication for operation. This is especially true in the presence of only mild digestive symptoms. These patients should be questioned carefully regarding the amount of dye ingested and retained. It should be remembered that some patients will fail to take all of the gallbladder dye as prescribed or may vomit a portion of the ingested dye. Similarly, in the presence of gastric retention from any cause or in delayed absorption in a variety of conditions, or diarrhea sometimes caused by the dye, a normal gallbladder will fail to visualize. For these reasons the dye should be reinforced, the conditions controlled, and the cholecystogram repeated. If the gallbladder fails to visualize at the time of the second examination, surgery may be recommended, provided that the symptoms are of sufficient severity and a complete x-ray survey of the gastro-intestinal tract has been noncontributory. Too much emphasis has been placed on poor filling, delayed emptying, or an unusual size or shape of the gallbladder as shown by cholecystogram (Fig. 224). In such instances, cholecystectomy is not advised unless the patient has had repeated attacks of typical gallbladder colic. A few patients with apparently normal cholecystograms who continue to have repeated attacks of severe colic deserve exploration and, despite the negative findings by x-ray examination, very small calculi may be found at the time of cholecystectomy and relief of symptoms obtained. Cholecystography is of limited value in the presence of jaundice because of interference with the concentration of the dye.

There is no better way to improve the results in biliary surgery than by stringent application of these criteria for operation. A complete gastro-intestinal survey is indicated despite clear-cut evidence of a diseased gallbladder by cholecystography. The frequency of serious associated lesions, especially neoplasms of the gastro-intestinal tract, demonstrates the wisdom of such thorough routine studies. Included among these are hiatus hernia, benign or malignant lesions of the stomach, carcinoma of the large bowel (especially the right colon) and, not uncommonly, pancreatitis.

Heart disease also must be considered as a cause of the symptoms. The initial distress from both gallstone colic and coronary heart disease frequently is referred to the epigastrium or substernal region and may be associated with shortness of breath. Such symptoms manifest in the middle of the night may be confusing and may account for delay in diagnosis.

Gallbladder disease not only mimics but may coexist with (and at times intensify) heart disease by precipitating congestive failure or aggravating symptoms of angina pectoris.[38] Although many physicians and most patients consider cardiac disease as a contraindication to surgery for biliary disease, cardiologists usually believe that it is beneficial to remove a diseased gallbladder, even though the patient has had a previous coronary thrombosis. Therefore, cardiovascular disease does not alter the surgical indications in acute cholecystitis, in recurrent colic from a diseased gallbladder or in suspected common duct stone. These patients do remarkably well if sufficient time is taken o stabilize the cardiovascular system properly prior to operation. It is good judgment o delay operation in the poor risk "cardiac" until the vital capacity exceeds 1,500 cc., and deally it should be greater than 2,000 cc.

There is no more grateful postoperative patient than the "cardiac" who has suffered repeated attacks of gallbladder colic over a period of years and previously has been denied the benefits of surgery because of fear on the part of the physician that the risk was too great. Furthermore, it is not uncommon to have the so-called "cardiac symptoms" regress after operation. The increasing age of our population makes this problem increasingly important.

"Silent Gallstones." Another controversial problem is the management of those patients with "silent gallstones." This group includes those patients in whom gallstones have been discovered unexpectedly either at the time of laparotomy for other diseases or as a result of a complete survey for gastrointestinal complaints. Some physicians feel that a policy of "watchful waiting" gives the best results. Others have questioned this attitude of accepting "silent gallstones" as essentially harmless to the patient because so many eventually develop a complication. The higher morbidity and mortality associated with complications of gallstones, particularly in the elderly, raises the question whether procrastination is actually safest or whether gallstones should be removed prophylactically whenever found.

In deciding whether cholecystectomy is in the best interest of the patient, the physician may be influenced by a number of factors. What is the size and the number of stones? Small stones which might obstruct the cystic duct or escape into the common duct are more likely to cause serious difficulties than the large solitary calculus. Are there symptoms from the stones? The physician must be constantly on the alert for the confirmed psychoneurotic with a gastric neurosis which originally led to the gastro-intestinal survey and demonstration of the gallstones. If a cholecystectomy is recommended in the hope of relieving all symptoms in such a patient, both physician and patient are doomed to disappointment.

Associated Disease. Will surgery benefit associated disease? Frequently, management of a duodenal ulcer is simplified after removal of a diseased gallbladder, since the ulcer type diet is tolerated more readily. Pancreatitis is associated frequently with biliary tract disease and, if recurrent, points strongly toward the presence of a common duct stone. The benefits to be expected in those patients with associated heart conditions have been stressed previously.

Obesity. Can the surgical risk be lessened? Gallbladder disease is found frequently in the overweight. Since there is a certain amount of surgical risk associated with obesity, it is always well to institute a weight-reduction program for such patients before elective surgery is undertaken.

Finally, if surgery is withheld, will there be future complications? The well-known trend of the general population toward higher age levels, together with the fact that the incidence of complications arising from gallbladder disease increases with each decade of life, makes it doubtful whether delay is actually safer for the patient.[4]

PREOPERATIVE EVALUATION AND PREPARATION

Laboratory Studies. Although the diagnosis of chronic gallbladder disease depends for the most part upon a thorough history and physical examination, together with a careful interpretation of the cholecystogram, there are certain laboratory studies which may be of assistance both in making a diagnosis and in determining the optimum time for operation. The number of preoperative studies obtained need not be great in number but are directly proportional to the patient's age, the severity of the disease, the presence of coexisting pathology or the complications of gallstones.

BLOOD COUNT. Necessary preoperative studies in all patients include a complete blood count which may disclose an unsuspected anemia requiring treatment or further study, or a leukocytosis, suggesting the presence of an associated inflammatory process.

URINALYSIS. A urinalysis with especial attention to the specific gravity and the measurement of the blood urea nitrogen are sufficient for estimating kidney function and may indicate dehydration or retention of nitrogenous wastes or unsuspected diabetes.

STOOL SPECIMEN. A stool specimen obtained at the time of routine rectal examination always should be examined for occult blood (guaiac test). If positive, additional steps must be taken to rule out an associated ulcerating lesion somewhere in the gastrointestinal tract.

PROTHROMBIN VALUE. The finding of a lowered blood prothrombin level indicates a need for vitamin K supplements, and the response to such therapy gives considerable information as regards liver function. Water-soluble and fat-soluble preparations of vitamin K are available for both oral and parenteral administration. A prothrombin value of less than 50 per cent of normal despite administration of vitamin K contraindicates operation[23] and suggests further liver-function studies.

NUTRITIONAL STATUS. A measurement of the total serum protein and the albumin-globulin ratio serves as a cross-index of the patient's nutritional status and may aid in evaluating hepatic function or hepatic reserves.

ICTERIC INDEX. Subclinical icterus is suspected if the icteric index is elevated in the patient without jaundice and suggests the presence of a silent common duct stone.

BLOOD AMYLASE. A determination of the blood amylase always should be included when a patient is seen early following an attack of biliary colic. If elevated, operation is best delayed for a considerable period following its return to normal.

Elderly Patients. Additional observations are required in elderly patients. These measurements are concerned not only with the diagnosis but also with the exclusion of pathology elsewhere.

COEXISTING DISEASE. Although many such patients present no special problem, a significant number of them have coexisting disease in other organs. As a matter of fact, the cause of the patient's complaints actually may be a lesion mimicking gallbladder disease. This is not surprising when one considers the sharp rise in the incidence of neoplastic and degenerative disease in patients past the age of 50. For these reasons routine sigmoidoscopic examinations together with complete barium studies of the gastro-intestinal tract are mandatory.

CONDITION OF HEART. Although a careful study of the heart is always required bef surgery, elderly patients require even m thorough investigation, which should incl an electrocardiogram and perhaps the 2-s exercise test in addition to the custom chest roentgenogram. It should be emp sized that the finding of a recent coron occlusion contraindicates operation, but e proved coronary artery disease, includin past history of infarction, need not de operation if there is no evidence of fail

GENERAL FITNESS. The vital capacity termination is a useful method of det mining cardiac as well as pulmonary funct in the patient's fitness in general. By keep a daily record, one obtains an index of progress of the patient's general vigor vitality in response to preoperative tre ment. Elective surgery will be tolera better if the vital capacity exceeds 2,000 but if it is below 1,500 cc., it might best to postpone operation. Priestley emphasized recently the importance of s cifically asking the patient to cough in or to detect the presence of secretion accu lated in the airways.[59] Steps can be taken remove excessive mucus so as to prevent minimize postoperative pulmonary com cations. These patients are urged to s smoking or at least drastically curtail t habit during the preoperative period.

BLOOD VOLUME DETERMINATION. Thi of particular value in those patients w have lost weight. On the average, a 1 cent decrease in the plasma volume is fou for every pound of weight loss. This ob vation is of particular importance si routine laboratory studies not infrequen fail to disclose these deficits. In the prese of weight loss, therefore, volume de should be anticipated, and an adequate nu ber of transfusions should be planned du the preoperative period to assure the tient's optimum condition at the time operation.

Some physicians are reluctant to trans the more elderly patients for fear of o burdening the circulation. This attitud probably no longer justifiable, since lim transfusions to 500 cc. per day, given slo offers little likelihood of embarrassing circulation. The benefits derived greatly weigh in importance the risk associated

xperience has shown that the pa-
decreased circulating protein are
nost likely to manifest shock dur-
tion or immediately thereafter.
re, poor wound healing and an
incidence of postoperative com-
must be anticipated in those
ith reduced blood volume.

y **Problems.** Urinary complaints
ost part are limited to the older
ents and when present call for an
of residual urine following void-
reful evaluation of the size of the
the possible obstruction of the
nd in most instances an intrave-
ogram are indicated in order to get
iled information of kidney structure
on. The measurement of an acid
se may be required to rule out as-
rostatic malignancy. Of more gen-
cation is the desirability of teaching
male patients to practice using a
bed prior to operation so that they
e faced with this problem for the
during the early postoperative
his will make voiding easier and
the unpleasantness and the possible
ions of catheterization. If actual
bstruction is present, urologic con-
is required, and a transurethral
may be indicated before elective
ectomy.

e Surgery. Since there is rarely a
urgency in deciding upon operation
ic cholecystitis, the time of surgery
election. In the younger age group
cute disease very little preparation
ry. In older patients where chronic
itis is associated with other dis-
nsiderable attention must be given
ated coronary, pulmonary, renal or
l disease.

y is one of the most difficult as well
on nutritional problems encoun-
patients with gallbladder disease.
ans and actuaries recently reported
mortality from all causes in over-
ersons was 150 per cent of the
value. Of even more importance,
ve mortality associated with such
surgical diseases as gallstones ex-
e expected mortality by over 200
The danger lies in the increased incidence of chronic disease of the heart, the arteries and the kidney, and especially delayed diagnosis resulting from the difficulties of accomplishing an accurate physical examination. Finally, the technical difficulties of operation, the increased incidence of anesthetic accidents, and the increased susceptibility to postoperative complications, i.e., collections of serum in the wound, atelectasis and thrombo-embolic disease, result in a poor candidate for operation.

Realizing the added surgical risk associated with obesity, a graduated weight reduction program should be instituted prior to advising elective surgery for gallbladder disease.

Time should be taken to prepare a chart which will permit the patient to record graphically his day-by-day weight trends.

The loss of 15 to 30 pounds may mean the difference between the success and the failure of the proposed surgery. When the will power of the patient is worn to the point where the weight curve remains stable or shows an upward trend, maximum benefit has been attained and it is time to proceed with operation.

Malnourishment. Of even greater concern to the surgeon is the problem of malnourishment. This is of particular importance preoperatively in those patients who have sustained a substantial loss in body weight as a direct result of a chronic disease process. The value of serial blood and plasma volume measurements in these patients cannot be overestimated. The initial correction of any deficiency in red cell mass frequently has proved to be of value in assuring a satisfactory response to any subsequent feeding program. Furthermore, since there are 30 Gm. of tissue protein for every gram of circulating protein, the total protein deficit may be calculated on admission and at intervals thereafter.[11] With the blood volume replaced and the protein deficit corrected, these poor risk patients may be operated upon with minimal risk and without the hazards of "chronic shock."

In any case, sufficient time must be taken whenever possible for adequate nutritional replacement, particularly of proteins, by mouth, by vein, or by one of the several methods of tube feeding, if such postopera-

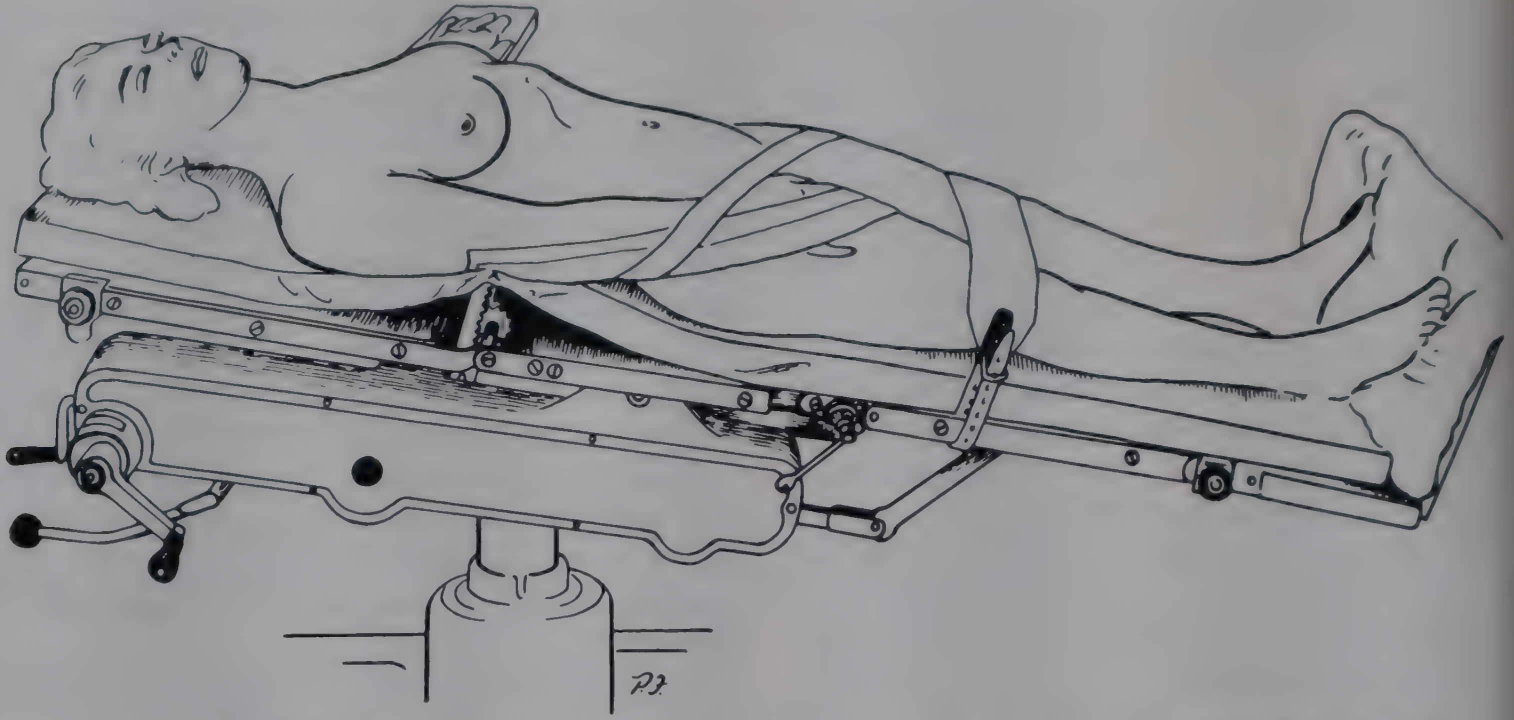


FIG. 225. The patient is placed well to the right side of the table, which is tilted laterally toward the surgeon and into reverse Trendelenburg position. Then the gallbladder rest, located under the xiphoid process, is raised from 2 to 3 inches. Particular attention must be devoted to protection of the patient from injury. A broad, padded strap is fastened loosely across the thighs just above the knees. The right arm should be taped securely to the thigh after the rest has been raised, so that it is not hyperextended at the elbow and does not slip off the edge of the table where pressure might produce nerve damage.

tive complications as retarded wound healing, sepsis, thrombo-embolism and the like are to be kept at a minimum.

A high-carbohydrate diet, glucose infusions and multiple vitamins given preoperatively aid liver glycogen storage and vitamin deposition. If the prothrombin time is below 50 per cent, 10 mg. of vitamin K are administered daily until this deficiency is corrected; in the meanwhile, other liver function studies are evaluated. Antibiotics are not given preoperatively unless some general systemic disease is present or technical difficulty is anticipated during dissection in the liver hilum where the risk of hepatic artery damage is increased. Vital capacity measurements and deep breathing exercises are practiced before operation so as to minimize the postoperative atelectasis which may occur in any upper abdominal surgery.

Preoperative Medication. This treatment should consist of drugs to reduce apprehension and to minimize sensitivity to pain, and other drugs to cause drying of secretions. For an average healthy patient 100 mg. of Demerol provides adequate sedation. This drug is selected in preference to morphine because there is a smaller incidence of nausea and vomiting following its use. Scopolamine (0.4 mg.) is the drug of choice for drying secretions. This also produces some amnesia and adds to the sedation produced by the Demerol. For very apprehensive patients Nembutal (100 mg.) may be administered in addition to the other drugs.

For the elderly and poor-risk patient premedication should be modified by using atropine instead of scopolamine, since there is less likelihood of producing postoperative delirium. The dose of Demerol should be reduced to 75 or even 50 mg., since elderly and poor-risk patients are more susceptible to the depressant effects of the narcotics.

A Levin tube is passed into the stomach routinely 30 minutes after giving the preoperative medication, and the stomach contents are aspirated before moving the patient to the operating room.

Position During Operation. This is most important in obtaining adequate exposure and making the technical procedure less difficult (Fig. 225). The patient is placed

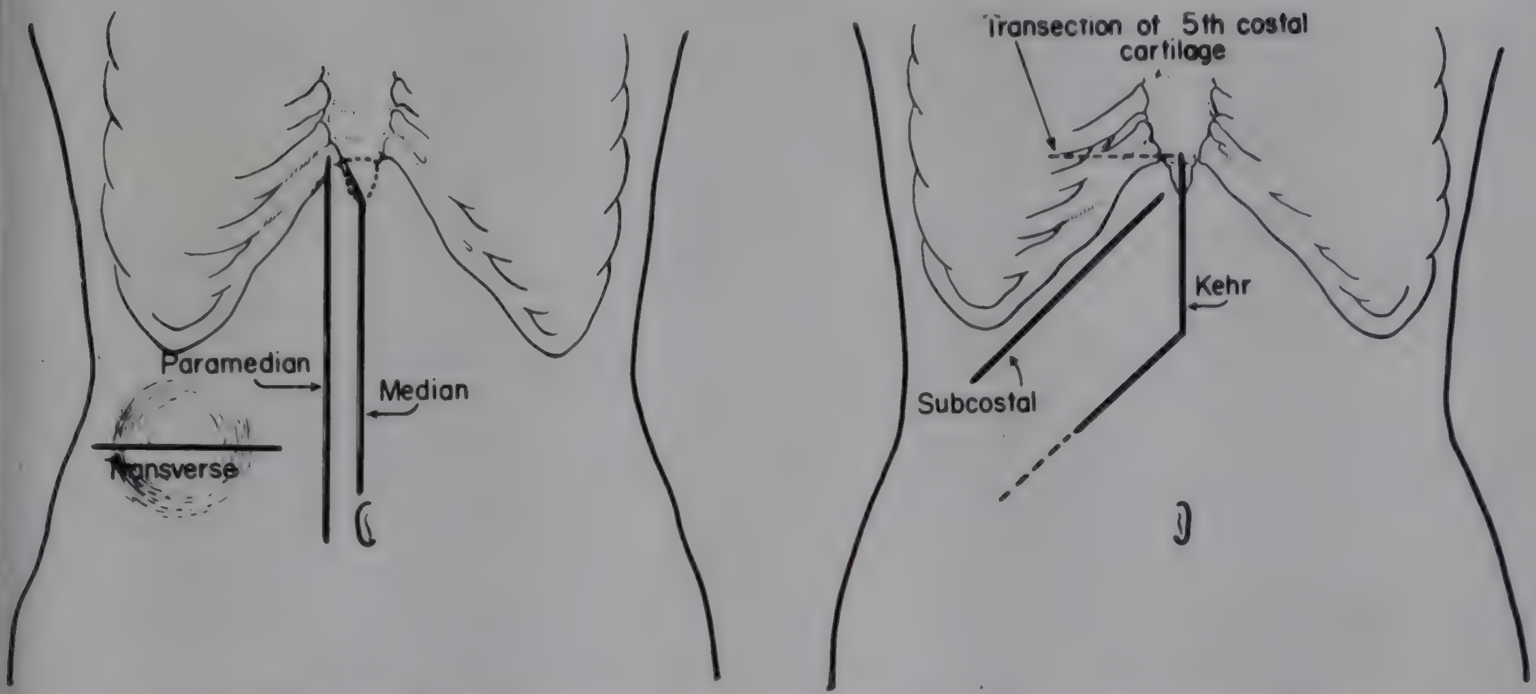


FIG. 226. The right paramedian and the oblique or subcostal incisions are utilized most frequently. The transverse incision offers certain advantages in the operative management of patients with acute cholecystitis and is of particular value if cholecystostomy is considered as the operation of choice. The mid-line approach through the linea alba releases the costal margin and allows for easier upward and outward retraction. If exposure is still limited, the xiphoid process is excised. The Kehr incision combines the advantages of both the vertical and the oblique incisions. The oblique position of the incision may be extended laterally through the oblique and the transverse muscles, or the costal cartilage opposite the fifth intercostal space may be transected.

well to the right side of the table. After anesthesia has been induced, but before skin preparation and draping, the operating table is tilted laterally toward the surgeon and into reverse Trendelenburg position. With the patient in this semi-erect position, the liver and the gallbladder tend to drop below the costal margin, assuring better exposure in the deeper portions of the liver hilum. In addition, the small and the large bowel with attached omentum fall away over the upper abdomen, thus minimizing the need for retraction. The gallbladder rest, located under the xiphoid process, is raised from 2 to 3 inches, allowing the surgeon to work more comfortably, with the gallbladder and bile ducts thrust forward.

Anesthesia. Choice of anesthesia for gallbladder surgery for an otherwise healthy patient must follow the principles of good anesthesia for any area of the body, namely, adequate premedication, smooth induction, good oxygenation, muscular relaxation and rapid recovery. The person administering the anesthetic must be sufficiently well-trained to be able to ensure these requirements and to cope with any complications, should they arise.

The choice of anesthesia in the otherwise healthy patient resolves itself into a selection of either spinal or general anesthetics. The good muscular relaxation provided by spinal anesthesia can be duplicated now with general anesthesia. While the selection of technic should be left to the individual anesthesiologist, general anesthesia is preferred by most.

Particular attention is paid to the patient with heart disease. If the patient has angina or coronary disease, anxiety regarding the procedure should be allayed by preoperative consultation and reassurance regarding the procedure to be performed.

It is particularly urgent in the presence of heart disease that episodes of anoxia, obstruction to respiration, and disturbances of blood pressure should not be allowed to occur. In this group of patients, hypertension may result in a cerebral vascular accident, and hypotension may result in acute coronary insufficiency, while a brief episode of anoxia may lead to serious or fatal complications because of insufficient oxygen supply to the already damaged cardiac muscle.

Regional anesthesia, local infiltration or nerve block may well be considered in the poor-risk patient. Intercostal nerve blocks between the fifth and the eleventh ribs will provide adequate anesthesia for cholecystostomy; this procedure may be accomplished also by local infiltration by the surgeon, either along the line of incision, in the skin, the fascia and the peritoneum, or by a field block along the lateral edges of the rectus muscle. If a more extensive procedure than a cholecystostomy is to be performed, the regional anesthetic should be supplemented by a splanchnic nerve block, so that desensitization of the visceral peritoneum may be accomplished. When operation is performed under local infiltration or nerve block it is usually desirable to administer sedatives intravenously during the course of the procedure. This may be accomplished by the use of very small doses of Pentothal Sodium or Nembutal Sodium in amounts sufficient to create drowsiness but not unconsciousness.

CHOLECYSTECTOMY

Incision

Although a variety of incisions have been proposed for gallbladder surgery, the right paramedian and oblique or subcostal approaches have been utilized most frequently (Fig. 226).

A paramedian incision extending from a point over the costal margin and to the right of the ensiform process to the umbilicus or below permits adequate exploration of the abdominal cavity and offers satisfactory exposure of the gallbladder and the extrahepatic bile ducts. It is best to avoid splitting of the rectus muscle because nerves and vessels are of necessity transected and, in turn, abdominal musculature is weakened, wound healing may be impaired, and the likelihood of a postoperative hernia is increased.

Proponents of the **oblique or subcostal incision** attest to equally good exposure and, in addition, minimal wound discomfort and a lowered incidence of postoperative hernias. However, its usage is limited to patients with a wide costal angle.

The transverse incision does offer certain advantages in the operative management of patients with acute cholecystitis and is of particular value if cholecystostomy is considered as the operation of choice. In these instances a small transverse incision is made directly over the palpable mass.

With the increasing incidence of operative injuries of the main biliary ducts, a number of incisions have been readvocated which permit better exposure of the common bile duct and nearby structures.

The mid-line approach through the linea alba releases the costal margin and allows for easier upward and outward retraction. If exposure is still limited, the skin incision may be extended upward and to the right, and the xiphoid process may be excised.

The Kehr incision, recently advised by Holman,[28] combines the advantages of both the vertical and the oblique incisions. The opening runs in the mid-line from the xiphisternum halfway to the umbilicus and then turns obliquely to the right and continues parallel to the midcostal margin; of necessity, the right rectus muscle is transected completely. If required, the oblique portion of the incision may be extended laterally through the oblique and the transverse muscles, or the costal cartilage opposite the fifth intercostal space may be transected.

Technic

In the absence of an acute suppurative infection involving the gallbladder the abdominal cavity is explored completely. The finding of a hiatal hernia is of particular importance inasmuch as it might explain a persistence of mild gastro-intestinal complaints (i.e., belching) following removal of a diseased gallbladder.

Having completed the abdominal examination, the right hand is passed over the dome of the liver, allowing air to enter the subdiaphragmatic space and permitting downward displacement of the liver. Then the gallbladder is inspected, and any adhesions between its under surface and such

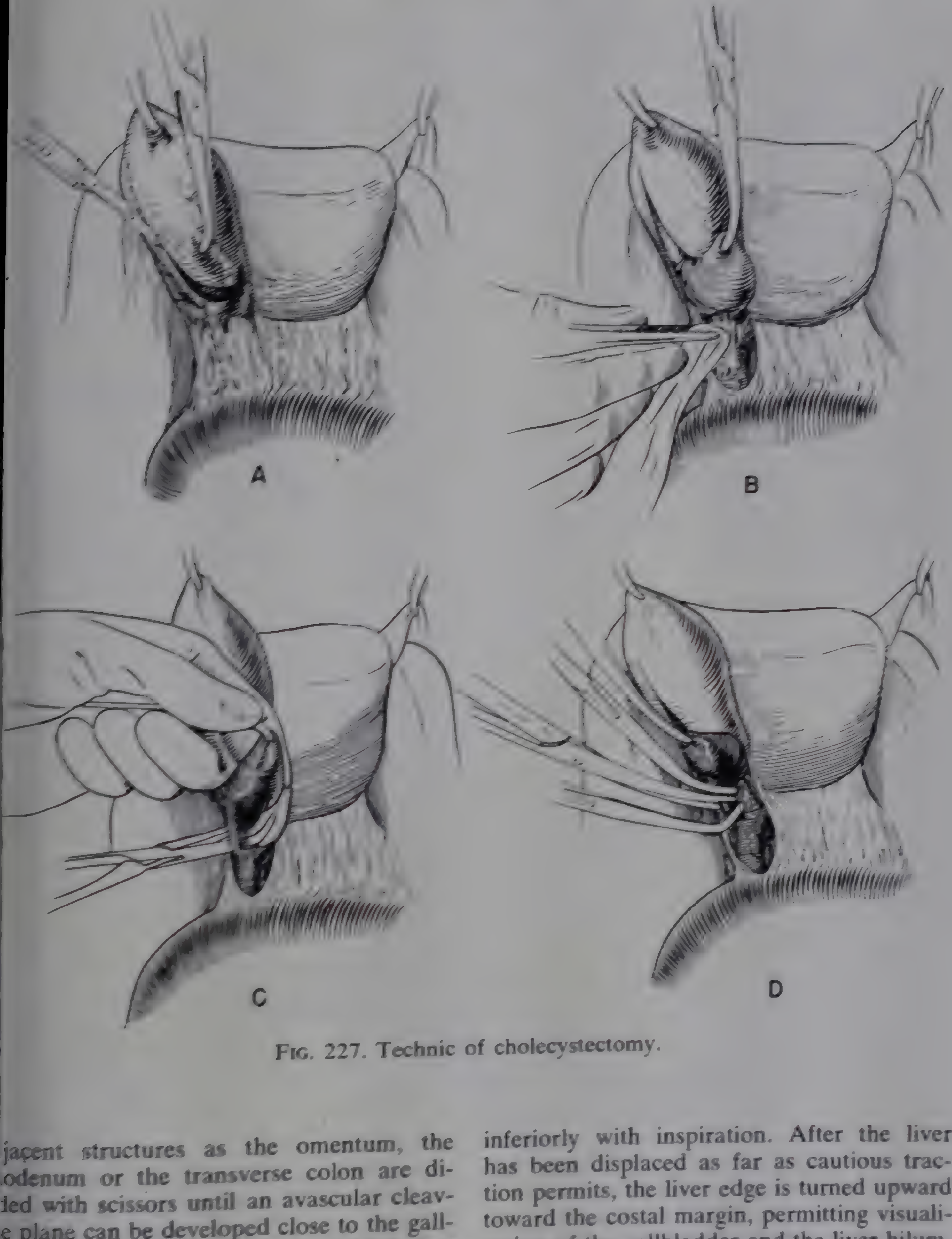


Fig. 227. Technic of cholecystectomy.

jacent structures as the omentum, the
odenum or the transverse colon are di-
ded with scissors until an avascular cleav-
e plane can be developed close to the gall-
adder (Fig. 227). Having established a
eavage plane, the remainder of the dissec-
on can be completed with blunt dissection.
The round ligament and the fundus of the
llbladder are grasped with clamps, and
ntinuous downward traction is applied.
action is exaggerated as the liver moves
inferiorly with inspiration. After the liver has been displaced as far as cautious traction permits, the liver edge is turned upward toward the costal margin, permitting visualization of the gallbladder and the liver hilum. If the gallbladder is acutely inflamed or distended, it is desirable to aspirate its contents through a trocar before clamps are applied to the fundus lest small stones be forced into the cystic or the common duct or the gallbladder be ruptured with contamination of

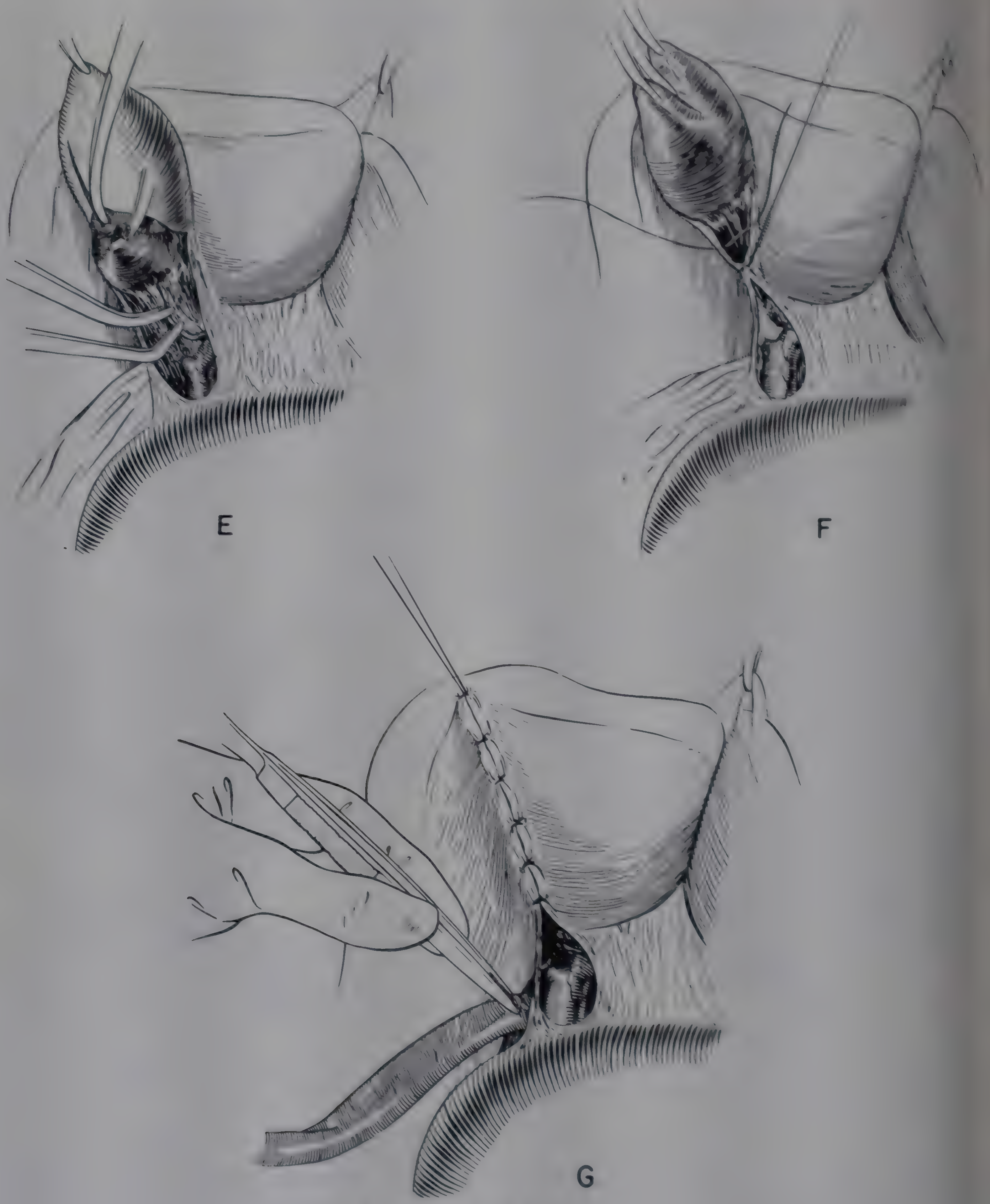


FIGURE 227 (*Cont.*)

the peritoneal cavity. The stomach, the duodenum and the transverse colon are now retracted laterally and downward with moist gauze pads held in position by a wide Deaver retractor at the lower edge of the wound.

The left index finger is inserted into the foramen of Winslow, and the region of the common duct is palpated for stones as well as for induration and thickening of the head of the pancreas. Then a moist gauze sponge is inserted into the region of the foramen of Winslow so as to prevent contamination of esser sac during the subsequent dis- n.

e undersurface of the gallbladder is ed with a second clamp at or just below iddle. The early placement of clamps hat is thought to be the ampulla should oided, because accidental injury to the ntified common duct may occur. This pecially true when the ampulla is large pendulous or when the gallbladder is ely distended, since the saccular am- bulges forward into the uppermost free on of the lesser omentum and may lie cent to and obscure the common duct a considerable distance. The ampulla, cystic and the common ducts must be sed and identified before a clamp may pplied safely to the ampullary region. hile maintaining gentle traction on the ladder upward and to the left, and g a small scalpel or long Metzenbaum ors, a peritoneal incision is outlined 1 from the liver edge, starting at the body extending downward along the right al border of the gallbladder fossa. In region of the ampulla and rather high, incision is directed medially across mann's pouch. The serosal incision lly is completed with long Metzenbaum cting scissors and then is continued nward along the free border of the he- duodenal ligament in order to expose upper portion of the common duct. g a long right-angled clamp and a tis- forceps, the dependent saccular portion he gallbladder is dissected carefully from upper portion of the lesser omentum, ng care not to damage the cystic or the mon bile duct. Once the ampulla has n defined clearly, the lowermost clamp be applied safely to the ampullary on.

Vith traction maintained on the ampulla he gallbladder, the cystic duct is defined means of gauze dissection. Next, a long t-angled clamp with narrow jaws is sed behind the cystic duct and between nd the cystic artery, first from the lateral then from the medial side of the gall- dder. A similar maneuver isolates the ic artery from the tissues about the com- n hepatic duct anteriorly and medially. surgeon should keep in mind the possibility of accessory vessels in the region of the cystic duct and should be familiar with the anomalous position and routes sometimes taken by the right hepatic artery. It is of particular importance to remember that the right hepatic artery lies parallel to and in close proximity to the cystic duct itself in nearly 1 out of every 5 patients and passes in front of the common hepatic duct in some 12 per cent of cases. With this in mind, the surgeon must not depend on palpation to determine the location of the cystic artery but must take the precaution of proving that the vessel enters the gallbladder so as to avoid mistaking an anomalous right hepatic or main hepatic artery for the cystic artery. Having identified the cystic artery accurately, a right-angled and then a half-length curved clamp are applied close to the gallbladder. The artery is divided between them and tied with a No. 00 silk ligature (Fig. 227).

Early ligation of the cystic artery has several advantages. In the first place, a relatively dry field is assured during the remainder of the dissection. In addition, it allows the convolutions of the cystic duct to be straightened out, permitting more accurate definition of the junction of the cystic and the common ducts. Finally, it eliminates the danger of serious bleeding from accidental injury or tearing of the cystic artery by traction on the gallbladder. The prevention of hemorrhage is most important inasmuch as a story of serious bleeding at the time of cholecystectomy is not infrequent in those patients who develop postoperative stricture of the common duct. The site of stricture in these instances is found close to the point where the cystic artery crosses over the common duct and suggests that in securing hemostasis the common duct itself had been clamped. It should be remembered that the cystic artery is the most probable source of hemorrhage during cholecystectomy; if vigorous bleeding occurs, it is controlled easily by compression of the hepatic artery between the thumb and the index finger of the left hand as it courses upward in the duodenal-hepatic ligament (Fig. 227). Having controlled the bleeding temporarily, the operative field is cleansed of blood, and, having visualized the bleeding point accurately, ligation may be accomplished without fear of injury to the ductal system.

After the cystic artery has been divided, traction on the ampulla places the cystic duct on tension, and its junction with the common duct is identified more easily. However, it should not be forgotten that excessive mobility of the common duct is a most important variation, and, when present, traction on the ampulla may tent the ductal system upward so that the common bile duct appears not unlike a prolonged cystic duct and may result in injury to or actual division of the common duct or the common hepatic bile ducts. Inasmuch as this anomaly is more common in patients on the very lean side, the surgeon must be constantly alert lest catastrophe occur during the course of an "easy" cholecystectomy. Additional anomalies of surgical importance include a short but wide cystic duct which invites trauma to the common bile duct. Failure to recognize an elongated cystic duct lying parallel to the main biliary duct accounts for a considerable number of retained cystic duct stumps in which stasis and subsequent stone formation may occur. Accessory cystic and hepatic ducts are not uncommon; if divided and overlooked, a temporary biliary fistula may result, and, more important, bile peritonitis or abscess formation with delayed stricture are also possibilities.

The cystic duct, having been isolated, must be palpated carefully to make certain that small stones are not present which might be crushed or forced into the common duct by application of clamps or remain unnoticed in the cystic duct stump. Any one of these 3 possibilities might be the basis for continued or recurrent symptoms following cholecystectomy. Small pieces of a crushed stone may be extruded into the common bile duct and act as a nidus for the later development of a common duct stone. A calculus knowingly forced into the common duct makes choledochostomy mandatory; if this is unrecognized, the surgeon may be hard pressed to explain biliary colic and perhaps jaundice in the early postoperative period. Lastly, a retained stone in the cystic duct stump may prove to be as incapacitating as the gallstones leading to the initial cholecystectomy.

It is very important to remove all common duct stones and ensure the patency o the papilla of Vater. Inasmuch as jaundice, is not a consistent or reliable sign indicatin when the common duct should be explored additional criteria must be established t minimize postoperative jaundice or symptoms from an overlooked common duc stone. It is imperative that the common duc be inspected and palpated to detect common duct calculi in all operations on th biliary tract. Some of the more commo indications for making a common duct exploration include: (1) palpable or visibl common duct stones, (2) enlargement o the common duct, (3) jaundice at the tim of surgery or a history of jaundice, (4 small gallstones, especially if the cystic duc is enlarged, (5) induration of the head o the pancreas that resembles pancreatitis o tumor, (6) light-colored bile with pigmen precipitates when the common duct is aspirated, (7) frequent attacks of severe gallstone colic, (8) pronounced involuntar vomiting, (9) recurrent symptoms afte cholecystectomy, or, (10) common duc stricture and other conditions requiring secondary biliary procedures.[55]

Choledochostomy or operative cholangiography may be accomplished by threading instruments or a small catheter through th cystic duct stump. Although this technic may give valuable information, difficulties may be encountered in introducing the necessar instruments past the spiral valve of Heiste or through the actual junction of the tw ducts. For these reasons, opening of th common duct may be preferred.

Having demonstrated the junction of th cystic and the common ducts and ascertaining that the common duct is not so angulated as to be injured and that it need not b explored, a long right-angled clamp is applied to the cystic duct so that not more tha a 1 cm. stump will remain following divisio of the duct. Although demonstration of th junction of the cystic and the common duct is ideal, if dissection is difficult, it is acceptable not to do so. A curved half-lengt clamp is applied above the right-angle clamp, and the cystic duct is divided between them. Then the cystic duct is ligate with a transfixing suture of No. 2-0 silk

care that the French needle passes
h the very edge of the duct but not
h its lumen. The stumps of the cystic
and duct are each inspected thor-
, and again the common duct is visual-
make certain that injury or angula-
as not occurred.
ng a scalpel, an incision is made in
rosa of the gallbladder about 1 cm.
he liver edge so that the liver bed may
peritonealized following enucleation
gallbladder. Gentle traction is applied
clamps on the cystic duct and the
lia, and the gallbladder is removed
its bed by curved-scissor dissection. If
ascular cleavage plane is identified, the
adder may be enucleated bluntly. Ac-
y blood vessels or bile ducts identified
the dissection are clamped and li-
The peritoneal flaps are approxi-
progressively as the gallbladder is
ved. Dry Gelfoam may be laid along
uture line if oozing is a problem. It is
able at this time to lower the gall-
er rest and once again inspect the op-
e site for bleeding or leakage of bile
e proceeding with closure. Incidental
ndectomy is permissible, depending on
perative risk and whether or not the
ndix can be delivered easily into the
tive field. A soft rubber drain is in-
d down to the foramen of Winslow and
ght to the outside through a stab wound
right of the incision. The stab wound
essed separately to facilitate subsequent
gement of the rubber drain and to
nize the soiling of the operative inci-
with bile or serosanguinous drainage.

POSTOPERATIVE CARE

scultetus or many-tailed binder is ap-
to the abdomen, preferably before the
nt recovers from the anesthetic.
jection of a long-acting local anesthetic
into the appropriate intercostal nerves
s to reduce incisional pain, and, in
the need for narcotics postoperatively
be reduced. This also facilitates cough-
nd minimizes postoperative respiratory
lications.
l patients in the older age group should
ven intranasal oxygen during the recovery period. It is imperative that a competent person be in attendance to keep close observation on the patient's airway. Removal of mucus by catheter suction at frequent intervals will be necessary until the patient is fully awake.

Nasogastric suction is continued for 24 hours postoperatively. A saline cathartic may be injected into the tube before it is removed. Fluid and electrolyte requirements are supplied daily by intravenous infusions of 5 or 10 per cent glucose in water. It is best to avoid saline during the first 48 hours postoperatively, since the kidneys may be unable to excrete any excess NaCl during this period. This is especially important in the aged patient so as to avoid embarrassing the circulation and to prevent collection of fluid in the tissues. Moreover, these patients have a negligible salt loss, so that replacement is not required. Starting on the second postoperative day, if the urinary output has been adequate, 2 or 3 Gm. of potassium chloride should be added to one of the liters of fluid.[17] This is the average maintenance dose and aids the return of normal intestinal function and recovery in general.

The quantity of intravenous fluid given on the day of surgery and on the subsequent 2 or 3 days should be limited to approximately 2,000 cc. One liter should be given in the early morning, and another should be started in the afternoon. An accurate record of the intake and the output must be kept. In those individuals who have lapses of incontinence, or if maximum accuracy is desirable, an indwelling urethral catheter must be used. Early ambulation where possible is routine.

The rubber drain is advanced, starting on the second postoperative day, and is taken out by the third day unless there is bile drainage. The presence of a drain is often painful, so it should be removed as soon as it has fulfilled its purpose. Skin sutures are removed usually on the seventh day, and the patient is discharged to his home by the eighth or the tenth day, barring complications. Inasmuch as the prophylactic employment of anticoagulant therapy is not practical, it is necessary to rely on a combination of measures to keep the incidence of venous thrombosis to a minimum. The in-

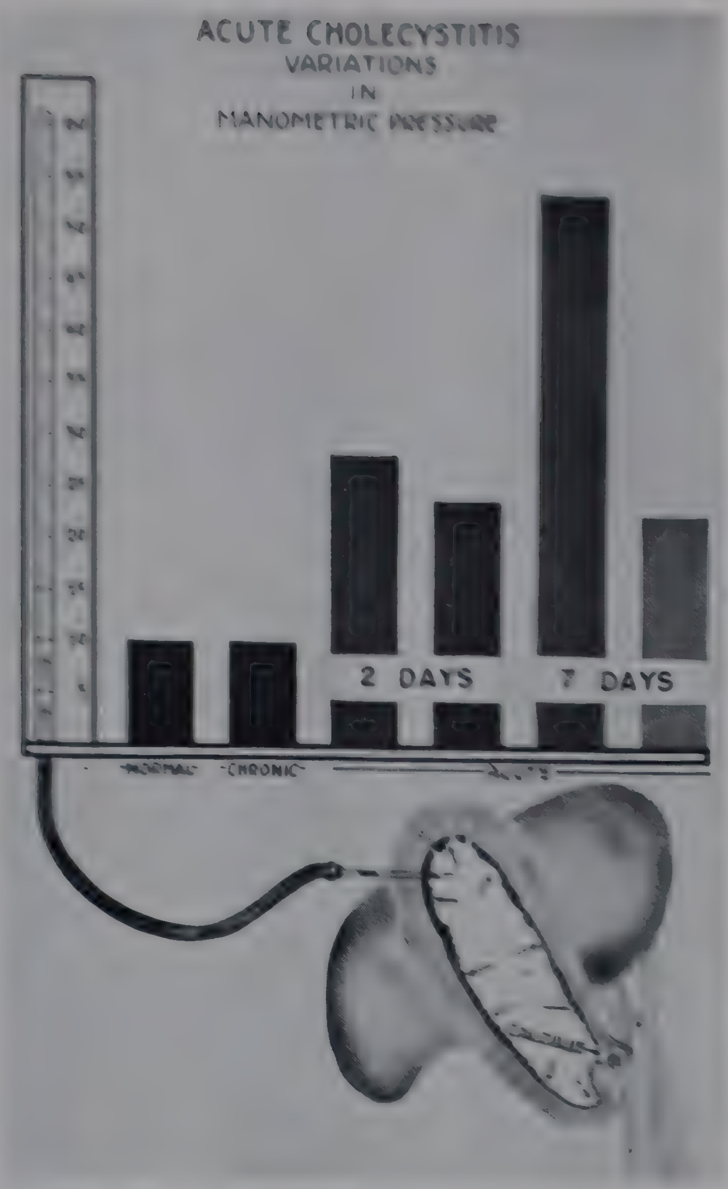


FIG. 228. Pressure measurements within the gallbladder at operation are increased greatly and are directly proportional to the duration of obstruction.

sistence by the nursing and medical staffs that the patient exercise his lower extremities while lying in bed and the employment of early ambulation are helpful. Elastic stockings, if snug fitting, will compress the superficial venous circulation so that blood flow is increased in the deep venous system of the lower extremities, where a large percentage of thrombi originate. However, these stockings should not be used in individuals whose arterial circulation in the lower extremities is compromised. Daily examination should be made of the lower extremities to rule out the presence of a deep venous thrombosis; if this is suspected, anticoagulant therapy should be instituted immediately.

ACUTE CHOLECYSTITIS

Acute cholecystitis is one of the more common and serious complications of cholelithiasis. From 10 to 12 per cent of primary biliary surgery is performed for this reason. Furthermore, there is a notable increase in the incidence of acute gallbladder disease in patients over 60 years of age. This is of particular significance, since the morbidity and the mortality entailed with cholecystitis are definitely increased in the older age groups.

Conflicting opinions regarding management and optimum time for operation in cases of acute cholecystitis have resulted largely from disagreement concerning the etiology and the pathologic process of the disease.

ETIOLOGY AND PATHOLOGY

For many years it was assumed that bacterial invasion was responsible for acute cholecystitis, and clinical treatment was based on this theory. However, studies in recent years have shown that the significance of an initial infectious process definitely has been overemphasized. Bacteriologic and histologic examinations frequently fail to demonstrate the presence of organisms, and smears or cultures taken at the time of operation from the wall of an acutely inflamed gallbladder or its contents are often negative.[5] While bacteria may play an important role in some cases of acute cholecystitis, in most instances infection is superimposed later upon already damaged tissue.

Investigations in recent years indicate that for the most part acute cholecystitis is the result of chemical irritation rather than a bacterial infection. Obstruction of the cystic duct by a calculus results in a marked concentration of the gallbladder contents. Initially, water and bile salts are absorbed, and an increase in bile pigments, calcium carbonate and cholesterol results. This concentrated mixture produces local irritation of the mucous membrane, increased osmotic pressure within the gallbladder, and marked distention and enlargement with a greatly thickened, edematous wall. Therefore, the gallbladder behaves not unlike a dialyzing membrane filled with a hypertonic solution

e measurements within the gallblad-
operation are greatly increased and
ectly proportional to the duration of
tion (Fig. 228). Although the con-
f such a gallbladder may appear to be
nt in nature, no bacteria can be dem-
ed by smear or culture, and the so-
"pus" is predominantly a concen-
chemical solution.

ystic duct obstruction is relieved, the
oms of acute cholecystitis subside
neously; however, residual inflamma-
nd scarring remain and predispose to
attacks. When obstruction continues,
ease is progressive, and acute gangre-
holecystitis may result. Bacterial in-
leads to empyema and sets the stage
rforation. The latter complication is
f the more serious complications of
cholecystitis and occurs in approxi-
12 per cent of these patients. Al-
n the presence of Rokitansky-Aschoff
s extending from within the gallblad-
the serosa may predispose to rupture
overdistention, this complication oc-
nost commonly as a result of vascular
ment and gangrene. Although the
gallbladder may become gangrenous,
angrene most commonly involves the
s, and in this instance free perforation
he general peritoneal cavity is not un-
on. If unrecognized, a suppurative or
peritonitis is inevitable. A large stone
ted in the ampulla may also lead to
re, but in this case localized abscess is
ule.

Clinical Picture

e typical case of acute cholecystitis is
osed clinically by severe pain, tender-
and muscle spasm in the right upper
ant, nausea and vomiting of varying
ity; fever and leukocytosis. A past his-
of recurrent attacks of biliary colic pre-
ted or made worse by fatty foods helps
elicited, but often there are no previ-
ymptoms referable to the gallbladder.
ould be emphasized that early in most
there may be only epigastric pain and
ernal distress associated with shortness
eath. These symptoms may so simulate
ac disease that the diagnosis of gall-
er disease is overlooked. Back pain or right shoulder pain associated with splinted respirations rather than shortness of breath should help sway the physician toward a diagnosis of acute cholecystitis.

A mass is not palpable early in the attack and there may be little clinical evidence other than mild tenderness to substantiate the diagnosis. Localized or rebound tenderness in the right upper quadrant with right rectus muscle spasm or rigidity appears when the overlying peritoneum is irritated. Elevation of the right costal arch produces pain, so that complete inspiration is difficult and painful. Percussion over the right costal margin or the right flank area may produce pain anteriorly in the gallbladder area. In some cases, the clinical syndrome may be obscured by symptoms from associated disease, such as acute pancreatitis, or is complicated by other consequences of acute gallbladder disease. If severe or seen late, dehydration or electrolyte imbalance comes to play an important role in the general clinical picture.

Laboratory Data and Roentgenographic Examination. Although there may be little or no change in the total white count in early acute cholecystitis, dehydration resulting from subsequent nausea and vomiting and the appearance of the inflammatory exudate leads to a marked leukocytosis with a high percentage of neutrophils. Reduction may be anticipated if proper hydration is accomplished, except in those patients with progressive disease; after fluid balance is established, the possibility of gangrene or a perforation of the gallbladder should be considered if the white count exceeds 20,000. If the obstruction is relieved spontaneously, the acute symptoms subside, and the white count returns toward normal.

Roentgenographic examination of the abdomen may show calculi or a hazy shadow in the right upper quadrant suggestive of an inflammatory mass. Inasmuch as the disease is primarily obstructive in nature, any attempt at visualization of the gallbladder by means of a radiopaque dye such as Telepaque is fruitless, either during or for several days following an attack of acute cholecystitis. However, cholecystography may be of value when the diagnosis is questionable. A gallbladder that visualizes and empties normally is not the basis of the patient's symptoms, and other systems must be investigated to explain the abdominal complaints.

DIAGNOSIS

Although in the majority of cases the diagnosis of acute cholecystitis may be established readily, other pathologic conditions may simulate the clinical picture. A flat and upright film of the abdomen and a chest roentgenogram are obtained in all patients. The visualization of calcified shadows in the gallbladder area suggests gallstones and may aid in establishing the diagnosis; in addition, other intra-abdominal or intrathoracic disease may be recognized or excluded.

Acute pancreatitis must be suspected in any patient with upper abdominal pain, and its frequent association with acute gallbladder disease makes it imperative to determine promptly the serum amylase levels in all acute abdominal episodes suspected or originating in the abdominal tract. Although an elevated serum amylase is diagnostic, these levels tend to fall to normal within 24 to 48 hours following the onset of the acute process. In those instances where the patient is seen relatively late in the course of the disease, it is helpful to study the amylase values on the peritoneal fluid obtained by simple lower mid-line peritoneal tap, using a 20-gauge spinal needle.[30] The peritoneal fluid amylase is sufficiently elevated and persists long enough to be diagnostic for as long as 6 days following onset. As little as 0.2 cc. is sufficient for examination. These confirmatory tests are invaluable, since a diagnosis of acute pancreatitis contraindicates early surgery. Examination of the peritoneal fluid is also of value in the diagnosis of suppurative or bile peritonitis. Smear and culture and tests for bile should, therefore, always be included in this study.

Although three out of four patients suffering an attack of acute cholecystitis will respond promptly to conservative management in the home, the remainder fail to show subsidence or show rapid progression and surgical intervention becomes mandatory. Since future complications are unpredictable, routine management is not satisfactory, and each case must be hospitalized as soon as the diagnosis is suspected.

Following estimation of the severity of the inflammatory process, the usual measures are taken to relieve pain and establish fluid and electrolyte balance. Small doses of Demerol or morphine and atropine, constant gastric suction for vomiting, and intravenous fluids for hydration are commonly included. No striking benefit is to be expected initially with antibiotics due to the fact that acute cholecystitis so often results from chemical irritation following sudden occlusion of the cystic duct rather than bacterial invasion. Intravenous Aureomycin may be helpful if a febrile course is due to suppurative cholangitis or hepatic abscesses associated with acute cholecystitis. The optimum time for operation depends on the severity of the disease process and the response to treatment. This calls for frequent reevaluation both by means of bedside visits and by laboratory aids.[47]

The vital signs, in particular the pulse, are determined every two hours and are preferably recorded on a graphic chart. A white and differential count is made every 4 to 8 hours, depending upon the severity of the disease. Frequent examinations and observations of the clinical signs and symptoms of the patient are made also. The limits of a right-upper-quadrant mass should be outlined on the skin of the patient, and this is useful for subsequent comparisons of size. The vital capacity is determined upon admission and several times daily as additional evidence of an expanding or decreasing process. A lowering of the vital capacity occurs as the gallbladder distention and the disease progress. An increase in temperature, pulse and respiratory rate, an increased white and differential count, a decreasing vital capacity, and persistent or increasing signs of pain and tenderness in the right upper quadrant are all indications of a progressive pathologic process. The presence of a well-defined mass in the right upper quadrant, increasing in size, is also indicative of progressive pathology with impending perforation. A probable gangrenous process with possible perforation should be considered if the white cell count is elevated to 20,000 or above, following hydration. It should be emphasized that the possibility of surgery must be considered whenever there is an unfavorable change in the vital signs, the white blood count and the ominal findings. Cardiovascular disease s not alter the surgical indications in te cholecystitis. The daily determination ital capacity is of particular assistance in ermining the optimum time for surgery he "poor risk" cardiac patient.

ptimum Time for Operation. This deci- n depends entirely upon the general con- on of the patient, the duration of time ce onset, and the progression of the patho- ic process as determined by the frequent luation of the clinical signs and symp- ns as well as the laboratory findings.[21] ere are no set rules or predetermined ssifications which fix the time when op- tion is to be performed. Certainly, routine nagement is unsatisfactory, and each case uld be evaluated and managed as an indi- ual problem.

Early cholecystectomy is preferred if the ient is seen within 24 hours and has been died for surgery within 48 hours after the set of an acute attack.[54] There is little nger of spreading infection at this time, ce the inflammatory process is most apt be chemical and not bacterial. In addi- n, surgery is made easier because an scular cleavage plane has developed al- dy between the edematous seromuscular ers of the acute gallbladder and facilitates enucleation.

Signs of generalized peritonitis call for gical intervention as soon as the patient's dition permits.

Those patients whose signs and symptoms l to respond or show rapid progression spite supportive treatment in the hospital ist be operated upon as soon as fluid lance is established (5%). Once again, an pending gangrene or perforation should be spected when the white count exceeds ,000. Free perforation, carrying a mor- ity 3 times that of localized peritonitis, relatively infrequent, since the omentum ually walls off the affected area. For this son, operation is more urgent in those tients with advanced signs and symptoms o have had previous abdominal surgery. omentum bound down in another part the peritoneal cavity offers no assistance sealing off the gallbladder region.

Some 15 per cent of patients who are ogressing satisfactorily under conservative atment develop an exacerbation of signs and symptoms.[54] A recurrence of pain sufficient to require narcotics, an increasing temperature, pulse or white count, or a decreasing vital capacity call for prompt surgery.

Operation is delayed and conservative measures are justified in those patients showing continued regression of their disease process (75%). Delay need not extend beyond 5 or 7 days, as it rarely adds to the safety of the procedure and may be detrimental to the outcome. Operation can be performed as a semielective procedure in an "improved risk" patient, while the cleavage planes developed by the acute inflammatory process in the wall of the gallbladder are still present and it is possible to do a complete cholecystectomy without excessive blood loss.

The mortality rate associated with acute cholecystitis will be improved if more patients are operated upon at any time during the day or night if, after fluid balance is established, they do not show evidence of continuous improvement under conservative management.

If the patient is seen late in the course of the disease with decreasing signs and symptoms or if he is an elderly "poor risk" patient, conservative management is justified as long as improvement is steady; then cholecystectomy can be performed as a semielective procedure at some later time.

With the increase in life span, the physician and the surgeon alike must consider the future consequences of recurrent cholecystitis and accept the responsibility of preventing other undesirable complications in the older age group. Although the mortality rate is higher for any surgical procedure in patients above middle age, a low mortality can be attained by careful preoperative and postoperative care, and there are only few contraindications to surgical intervention for acute cholecystitis, regardless of age. It is apparent that the optimum time for recommending surgery is before or during the early stages of this disease when the patient is a better risk and free of complications. This fact should be given careful consideration by those physicians who see patients with their initial attack of acute cholecystitis.

Complications of acute cholecystitis include gangrene and perforation of the gallbladder with local or generalized peritonitis or the formation of an internal biliary fistula which may result in intestinal obstruction (gallstone ileus). Spontaneous external biliary fistulae occur only on rare occasions.

GENERALIZED PERITONITIS. Those patients with a generalized peritonitis on admission whose signs and symptoms fail to respond or show rapid progression despite supportive therapy must be operated upon as soon as fluid and electrolyte balance is established.

PERFORATION OF GALLBLADDER. If the patient is seen late after perforation, attention must be given to the correction of dehydration, electrolyte imbalance and blood volume deficit, if a mortality is to be avoided. A wide-spectrum antibiotic is started in heavy doses. Human serum albumin and whole blood usually are required to restore the diminished blood volume, and it is best to delay surgery until the pulse rate has fallen below 120 and the blood pressure has stabilized at near normal levels. The surgical procedure of choice is cholecystostomy, and in only rare instances and in exceptionally good risk patients is cholecystectomy advisable.

LOCALIZED ABSCESS. Perforation of the ampulla leads to a localized abscess in the right subhepatic space adjacent to the gallbladder but may result in contamination of the lesser pouch, the space between the liver and the diaphragm or the right peritoneal gutter. In these instances, the patient's presenting symptoms may be those of a subphrenic, a right lower quadrant or pelvic abscess rather than those of an acute cholecystitis. Localized peritonitis should be suspected if an inflammatory mass is palpable; when present, cholecystostomy and incision and drainage of the abscess should be performed.

GANGRENE AND INTERNAL BILIARY FISTULA. If one of the hollow viscera becomes adherent to the gangrenous area and if the inflammatory process continues to progress, perforation may occur in the duodenum, the colon and, more rarely, the small bowel. Although closed or adhesive perforation of the gallbladder is not considered as a common complication of cholecystitis, an internal biliary fistula is found in some 3 per cent of all patients with biliary tract disease. It is the large, solitary gallstone that is most likely to erode into the bowel. The initial picture is that of an acute cholecystitis with severe right upper quadrant pain and tenderness, nausea and vomiting and, in most cases, an inflammatory mass. When perforation occurs, the symptoms subside but may be followed by new complaints, depending upon the location of the perforation and the size of the gallstone. Reflux of intestinal contents into the biliary tree leads to an ascending cholangitis characterized by chills and fever and progressive liver damage. The diagnosis cannot be made by cholecystography, but a flat film of the abdomen or an upper gastro-intestinal series may show air or barium in the biliary tree (Fig. 229). If an internal biliary fistula is suspected, antibiotics are indicated in anticipation of an ascending infection, and it is best to delay operation until the acute inflammation and the edema about the fistula subside. Definitive therapy consists of removal of the gallbladder and elimination of the fistulous tract.

GALLSTONE ILEUS. The major concern after formation of an internal biliary fistula is the gallstone which, having ruptured into the duodenum, traverses the proximal small bowel, but its size prevents its passage through the distal ileum, resulting in an acute intestinal obstruction (gallstone ileus). As one might suspect, these patients are gravely ill, especially if the disease is allowed to progress without recognition and treatment. The diagnosis always should be considered in patients with acute small bowel obstruction and a past history of gallbladder disease, and history of spontaneous recovery from a severe gallstone colic or symptom suggesting an acute cholecystitis prior to the onset of abdominal cramps and distention.

X-ray examination of the abdomen may demonstrate air in the biliary tree, and on occasion a radiopaque gallstone may be seen in the right lower quadrant (Fig. 229). Treatment is aimed at surgical relief of the obstruction by removal of the gallstone from the terminal ileum. At operation, the stone may be manipulated past the ileocecal valve; however, in most instances, enterotomy will be required. The presence of a second gallstone in the intestine must then be excluded. The area of the biliary fistula should not be disturbed for fear of rupture into the peri-

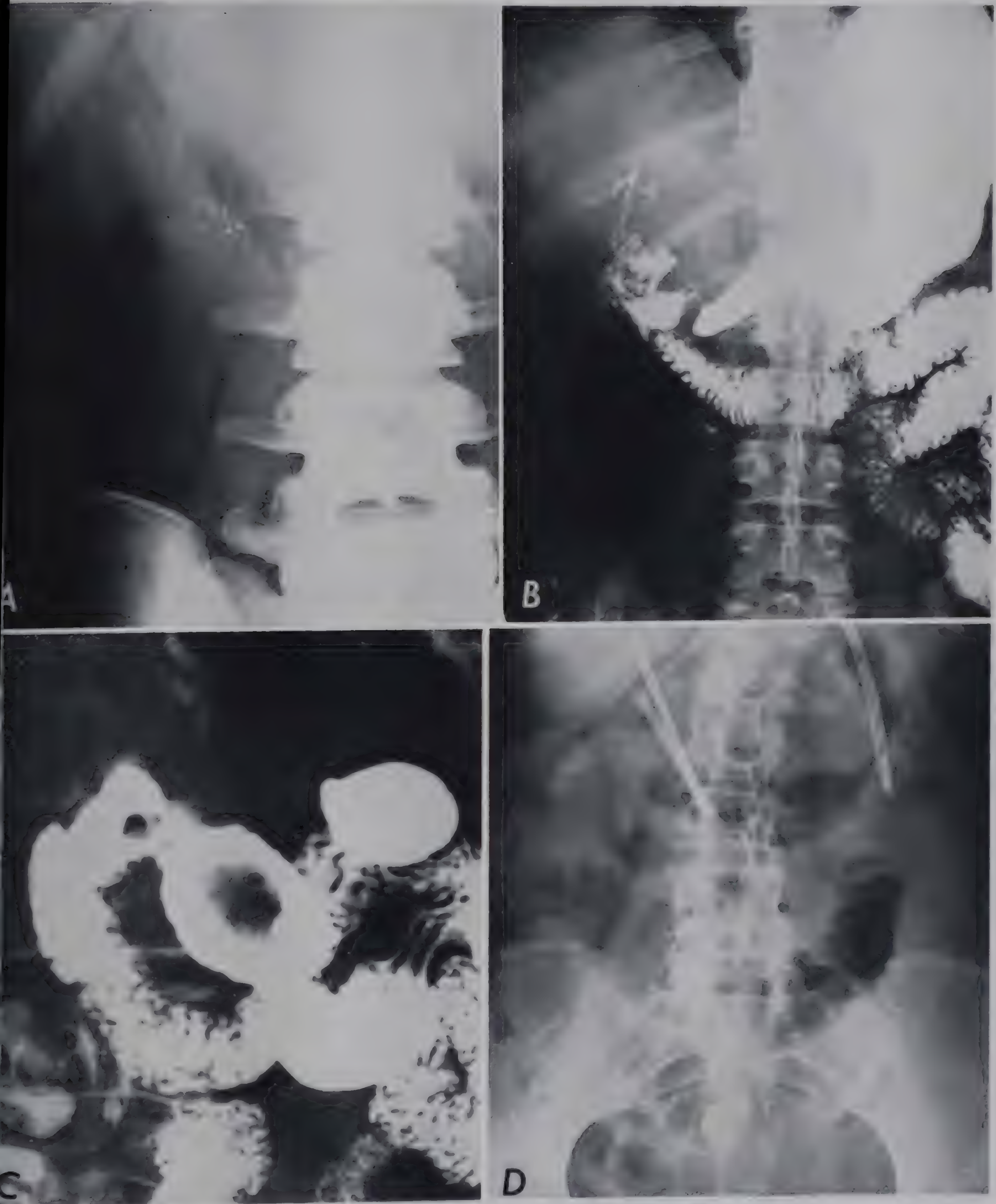


Fig. 229. Internal biliary fistulae. X-ray examination of the abdomen may demonstrate (A) air or (B) barium in the biliary tree. (C) Large solitary gallstone outlined in duodenum by barium swallow. (D) Gallstone ileus. Note radiopaque gallstones in the right upper quadrant and near the mid-line anterior to the sacrum. The latter stone has impacted in the terminal ileum.

neal cavity and secondary peritonitis, and moval of the gallbladder and eradication the fistulous tract should be performed at me future date.

Gangrene and External Biliary Fistula. A gangrenous gallbladder may become attached to the anterior abdominal wall and, having perforated, produces an abscess which presents beneath the anterior parietes. When the skin is broken or incised, bile, gallstone and purulent material drain out, and an external biliary fistula is formed. As in the case of cholecystostomy, the fistula is self-limiting and seals over after the acute inflammatory process subsides. However, if common duct stones and other causes of obstruction exist, the fistula may continue to drain a large amount of bile. Cholecystectomy at a time of election should be performed in either case.

Emergency Operations on the Gallbladder. For the *acutely ill patient* in whom operative intervention is urgently necessary, enough time should be allowed in the preoperative period to restore hydration and build up the blood volume. This will prevent an acute hypotensive crisis during the induction of anesthesia or shortly after the beginning of the operation.

As with other emergency operations one of the greatest hazards related to the anesthetic is the danger of aspiration of vomitus. Patients having emergency procedures must be presumed to have food in the stomach. Although a valuable aid in decompression, the stomach tube cannot be relied upon to remove completely all stomach contents, particularly the larger pieces of food. For this reason all emergency patients must be regarded as potentially in danger of aspiration of vomitus. Among the necessary precautions under these circumstances are the presence of strong and working suction and the availability of a cuffed endotracheal tube for immediate insertion.

The patient who requires an emergency operation on the gallbladder, if he is in relatively good general condition, may be treated by the anesthetist, as outlined above for a good-risk patient. On the other hand, if the general condition has deteriorated greatly, then the anesthetic should be administered in accordance with the considerations outlined for the poor-risk patient.

Operation for Acute Cholecystitis. Although classical cholecystectomy is feasible in the majority of patients with acute cholecystitis, the procedure of choice generally cannot be determined until the peritoneal cavity is opened and the exact pathology evaluated. Exceptions include the elderly or poor-risk patient with an easily palpable and well-defined mass in the right upper quadrant or whose general condition is such that formidable operation seems to be unwise or is contraindicated, regardless of operative findings. Under these circumstances, decompression of the gallbladder, removal of the obstructing calculus and institution of drainage by cholecystostomy is the preferred method and on occasion proves to be lifesaving.[18]

Cholecystostomy or simple drainage of the gallbladder is also advisable when a walled-off abscess is encountered about the gallbladder and always should be considered if technical difficulties are anticipated by the surgeon.

Partial cholecystectomy, leaving intact that part of the gallbladder adjacent to the liver, also may be of value and should be given due consideration in those instances where the gallbladder is gangrenous or is buried so deeply in the liver tract that cholecystectomy might be hazardous. This is a safe and satisfactory technic and offers as good a mortality and end result as cholecystectomy; in a large percentage of cases it will eliminate the need for a complete removal of the gallbladder at some future date. The finding of many dense adhesions attached to the under surface of a thick-walled, tense, edematous gallbladder in a good-risk patient is sufficient indication for cholecystectomy from the fundus downward,[12] thus avoiding the possibility of accidental injury to the common duct or right hepatic artery.

RETROGRADE CHOLECYSTECTOMY. In most cases of acute cholecystitis, removal of the gallbladder by the retrograde method can be accomplished without troublesome bleeding if advantage is taken of the subserosal cleavage plane produced by inflammatory edema. If this dissection plane cannot be found, injection of saline under the gallbladder serosa may define its limits more easily.[10] The severely distended gallbladder may require decompression by aspiration of contents with a trocar inserted through the fundus. This procedure facilitates removal of the gallbladder, avoids accidental rupture with contamination of the peritoneum with bile and pus and prevents small cystic duct stones from being forced into the common duct. As the trocar is removed, a curved p is applied to the fundus of the gall- der to aid traction and to seal off the ar wound. A routine culture of the aspi- d material always must be made. Adhe- s to the colon, the lesser and the greater ntum are divided by blunt and sharp dis- ion, exposing the hepatoduodenal liga- t and the foramen of Winslow. Then one proceed with the classical cholecystec- y; however, potential dangers must be in mind constantly. In the first place, gallbladder may be avulsed from its bed oo much traction is applied before the sa is incised. If a sufficient cuff of tissue ot developed, closure of the liver bed will difficult or impossible and it may con- e to ooze blood and bile. Second, there onsiderable danger of injury to the com- n duct if clamps are applied to the region the distended ampulla of the gallbladder ore it has been isolated from the adjacent ctures. Finally, the common duct, the tic duct and the right hepatic artery may drawn up into an unusual position as a ult of the inflammatory process, and in- is likely to occur unless one carries out ery meticulous dissection.

Therefore, in many instances it is desir- e to evacuate the contents of the gall- dder and remove it from the fundus wnward in order to identify and ligate re easily and safely the cystic duct and ery. With the fundus of the gallbladder racted upward, an incision is made through edematous serosa, starting at the fundus extending downward on either side about m. from the liver substance. The inflam- tory edema of the wall of the gallbladder ilitates enucleation, inasmuch as it de- ops a relatively avascular cleavage plane ween the serosa and the fibromuscular ers. The importance of incising the serosa ly cannot be overemphasized because the tely inflamed gallbladder may be torn m the liver, leaving an oozing raw liver face. The cuff of thickened gallbladder ll at the margin of the liver is grasped h a curved hemostat for retraction while gallbladder dissection is completed. The er bed is closed as the dissection pro- esses so as to minimize oozing throughout remainder of the procedure.

As an alternate method, the opening in fundus is enlarged, and the left index finger is inserted. As in dissection of a hernial sac, counterresistance may be of some help in freeing up the inflamed viscus.[41]

The serosal incisions are lengthened down to the region of the ampulla and, inasmuch as the cystic artery is still intact, all bleeding points must be controlled accurately or troublesome hemorrhage will result. If, for any reason, the raw liver surface is exposed, sutures of fine silk on thin curved needles are passed deep into the liver substance and tied carefully so as to compress the bleeding vessels but not tear the liver substance. Great care must be taken in isolating the ampulla of the gallbladder from the common duct.

It should be remembered that traction made on the mobilized gallbladder will be almost entirely upon the cystic artery; if this is continued or excessive, the vessel will tear at a place near its point of origin from the right hepatic and produce vigorous bleeding. Therefore, the cystic duct must never be clamped and cut until the cystic artery has been identified, divided and securely ligated. Furthermore, excessive traction must be avoided at all times.

The cystic artery, which is considerably larger than normal in acute cholecystitis, is isolated from the cystic duct with the usual right-angled clamp, but no attempts are made to separate the vessel from the indurated tissue around it. The right hepatic artery should be identified accurately lest it be clamped and divided. The cystic artery and adjacent tissues are divided and ligated carefully with a transfixing suture of No. 2-0 silk.

Attention is now directed toward the cystic and the common ducts. It should be emphasized that common duct stones are not infrequent in the presence of acute cholecystitis. A stone impacted in the cystic duct does not preclude additional stones in the common duct, especially if the cystic duct is large and the stones in the gallbladder are small in size. In any case, the cystic duct is now divided and tied with a transfixing suture of fine silk; because if choledochostomy is to be included, removal of the gallbladder leads to a better exposure of the common bile duct. The operative site is inspected repeatedly for oozing, and a Penrose drain is inserted down to the region of the cystic duct before closure.

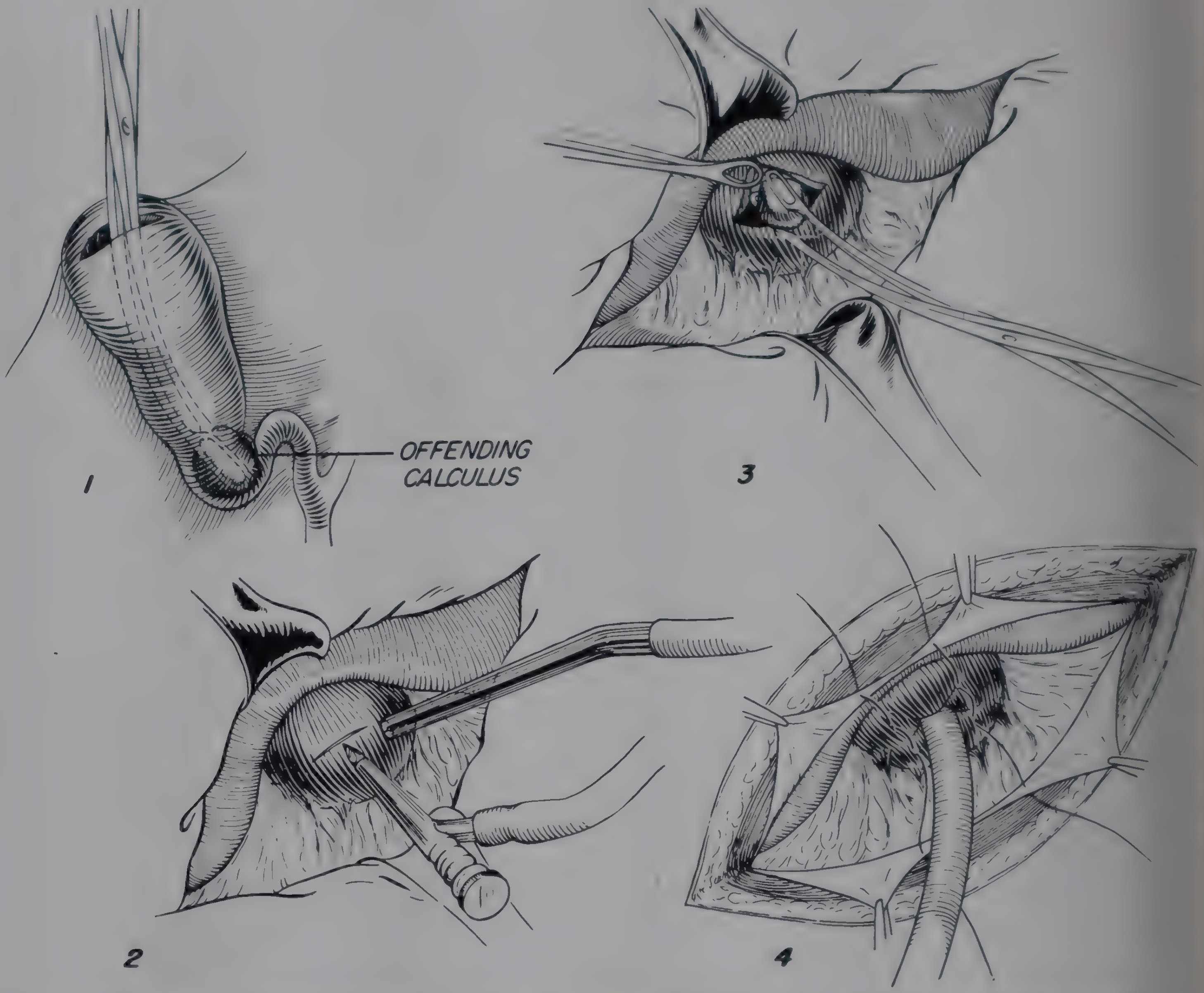


Fig. 230. Cholecystostomy, while no longer recognized as a routine method of treatment for patients with chronic cholecystitis and gallstones, may prove to be life-saving in the presence of a fulminating infection of the gallbladder. Under procaine anesthesia, if necessary, a small transverse or oblique incision is made directly over the tender mass in the right upper quadrant so that its midportion will be directly over the maximum point of tenderness.

Cholecystostomy. Cholecystostomy, while no longer recognized as a routine method of treatment for patients with chronic cholelithiasis and gallstones, may prove to be lifesaving in the presence of a fulminating infection of the gallbladder. Although subsequent cholecystectomy and exploration of the extrahepatic bile ducts may be required after the infection has subsided and the patient is in better physical condition, the over-all mortality in the aged or poor-risk patients with acute cholecystitis will be lowered. In addition, cholecystostomy should be considered in similar risk patients, where removal of calculi is necessary because of repeated bouts of colic. Finally, on rare occasions and in the presence of longstanding obstruction of the common duct and of total jaundice, hepatic failure may be avoided by preliminary drainage of the biliary tract by means of cholecystostomy. Definitive operation may be considered after the jaundice has subsided and the patient's general condition has improved.

Not infrequently, therefore, an over-all evaluation of the patient suggests that cholecystostomy is the operation of choice. Having made this decision, and with the patient under procaine anesthesia, if necessary, a small transverse or oblique incision is made directly over the tender mass in the right upper quadrant so that its mid-portion will

rectly over the maximum point of ten-
ess. Occasionally, when technical diffi-
es or the severity of the infection in-
ng the gallbladder is not suspected
ous to a planned cholecystectomy, it
be necessary to carry out cholecystos-
through the usual right paramedian
ion.

o effort is made to dissect the adhesions
the under surface of the gallbladder.
fundus of the gallbladder is walled off
moist gauze pads in preparation for
uating its contents. An incision is made
ugh the serosa at the apex of the fundus,
a trocar is thrust through the thickened
natous wall to remove as much of the
id contents as possible (Fig. 230). Con-
t suction is maintained adjacent to the
ning as the trocar is withdrawn. A cul-
is taken routinely. After the trocar is
drawn, the edematous wall is grasped
Allis clamps, and the opening in the
dus is enlarged. A suction tip may be
oduced into the lumen of the gallbladder
emove any remaining liquid or grumous
erial. Almost invariably one finds an im-
ted stone in the ampulla or the cystic
t, and an effort must be made to remove
ensure drainage of the infected biliary
ts. On occasion, large ampullary stones
be displaced upward by compression of
ampulla between the fingers. If unsuc-
sful and if the stones cannot be dislodged
a small flexible scoop, a fenestrated
ney stone forceps may be used. If this
fails, no further attempt is made to
ove the calculus, since the operation
uld not be prolonged needlessly.

The lumen of the gallbladder is now
hed repeatedly with normal saline to
h out any remaining debris, and a small
ber catheter is inserted down to the re-
of the ampulla and anchored to the
dus with an interrupted suture. A pre-
usly placed purse-string suture of No.
silk is tied snugly about the drainage
e. If the infection is severe, or if an ab-
s has been encountered, a rubber tissue
in is inserted along the wall of the gall-
lder. The fundus is anchored to the peri-
eum to prevent escape of gallbladder
tents into the peritoneal cavity before
area has sealed off. Then a routine closure is effected, and after a sterile dressing is applied, the catheter is anchored to the skin with a suture or adhesive tape and is connected to a drainage bottle.

Following operation the patient is maintained in a semi-Fowler position, fluid and electrolyte balance is maintained by intravenous infusion, and the indicated antibiotics are administered. Otherwise, the postoperative management is the same as that described under cholecystectomy for chronic cholecystitis. Removal of the rubber catheter depends upon the amount and the nature of the drainage and the general condition of the patient as determined by the pulse rate, the response of the vital capacity and the white blood count. In any event, a cholangiogram must be made for evidence of overlooked calculi in the region of the ampulla, the cystic duct or the common duct while the tube is still in place. If the general condition of the patient is good, and if postoperative recovery proceeds without complications, a definitive cholecystectomy may be performed approximately 2 weeks after the initial drainage. Elderly patients seriously ill from associated diseases should be sent home to be readmitted after 3 to 4 months for re-evaluation. If the patient's condition has not improved, cholecystectomy is not recommended.

PARTIAL CHOLECYSTECTOMY. An acute, gangrenous gallbladder or one so deeply buried in the liver that cholecystectomy seems to be hazardous may be resected partially, leaving intact that portion adjacent to the liver. As far as can be determined there is no harmful effect from the remaining gallbladder wall.

Having mobilized the gallbladder as for cholecystectomy from the fundus downward, the anterior wall is excised down to the region of the cystic duct, which may or may not be ligated. When the cystic duct is not ligated, an attempt is made to insert a small catheter for bile drainage, which is anchored in position with a transfixing suture. Any bleeding about the thickened, edematous gallbladder wall is controlled with either a continuous stitch or interrupted sutures. Although efforts have been made in the past to destroy the remaining mucosa, by either actual cautery or the application of some fixative, such as phenol or Carnoy's solution, it probably is unnecessary. No attempt is made to explore the common duct, even though a few patients will require reoperation. Several large Penrose drains are introduced down into the region of the cystic duct and brought out through a stab wound to the right of the incision. The omentum is turned upward into the operative site, and the wound is closed in routine fashion. Stay sutures are advisable in most instances.

A postoperative cholangiogram should be taken in those instances where a catheter has been inserted into the cystic duct to ascertain whether or not a common duct stone is present, necessitating a second operation after the infection has subsided.

COMMON DUCT STONE

INCIDENCE

One of the most common and serious mistakes in surgery of the biliary tract is the surgeon's failure to establish the presence of and remove calculi in the intrahepatic and the extrahepatic bile ducts. Failure to suspect the presence of ductal pathology, lack of appropriate instruments and fear of increasing the morbidity and the mortality are largely responsible for this error of omission.

Autopsy and clinical statistics have been reported indicating that approximately 20 per cent of all cases of cholelithiasis have one or more stones located in the biliary ducts exclusive of the gallbladder and the cystic duct. Indeed, choledocholithiasis is the most common complication of gallstones, and as life expectancy increases, its incidence may rise still further for several reasons. Biliary calculi increase with successive decades of life, and, more important, the longer stones are harbored, the greater the chance that one or more will escape into the common duct. A comparison of the end results in patients over and under the age of 50 suggests the advantage of advocating operation at an earlier age instead of delaying surgical treatment until this or other complications develop.[38]

SYMPTOMS

The symptoms of common duct stones are quite deceptive and in a few instances may be so insignificant as to be overlooked
the absence of jaundice. Although no in
vidual sign or symptom constitutes an abs
lute indication of common duct stone.
careful evaluation of a number of these offe
a satisfactory method.

DIAGNOSIS

Certainly the diagnosis of stones in t
biliary ducts should be considered in patien
with a history of epigastric pain and
colic, jaundice, pronounced and spontaneo
vomiting or intermittent chills and fev
particularly when associated with a past h
tory of cholecystic disease.

The location of the initial pain and f
quency of attacks should be noted carefu
in every patient with suspected cholelithia
because each may offer valuable clues
garding the presence and the position of t
calculi. Pain which begins and persists
the epigastrium is strongly suggestive th
a stone is distending either the cystic or t
common duct (Fig. 223). Frequent and
peated attacks of colic imply that multi
small stones are being passed through t
cystic duct into the common duct. Sp
taneous and pronounced vomiting acco
panying a gallbladder attack is also sign
cant in establishing the provisional diagno
of choledocholithiasis, even in the absence
jaundice, and occurs in over three four
of the cases.[49] Nearly 1 out of every 4
these patients presents himself with such
marked loss of weight that, when associa
with jaundice, a diagnosis of malignan
may be suggested.

Common duct calculi without stones
the gallbladder are uncommon but may
found after cholecystectomy, due to ov
looked common duct stones or to cal
retained in a cystic duct stump.

Chills and fever, implying an ascend
cholangitis, may accompany the attacks
biliary colic or occur without colic, an
severe and unrelenting—particularly in
presence of jaundice—are an indication
early operation.

All too frequently the surgeon disreg
the diagnosis of common duct stone and
to consider seriously the exploration of
bile ducts for calculi during cholecystect
unless the patient is jaundiced at the tim

zation or operation. Because the re- biliary surgery can be improved if common duct stones remain after stectomy, it is important to empha- w silent and atypical they may be. recently reviewed series there was ory of jaundice in 35 per cent; there past history in 21 per cent, and at the f operation only 44 per cent were ed[22] (Fig. 231). Of equal impor- common duct stones were removed r than 3 out of 4 patients with gall- who were jaundiced while in the l. It must be recognized that stones ccur in the common duct without panying jaundice, and that other cri- han the presence of jaundice are nec- for common duct exploration in order d overlooking any existing common stones. Distended and/or thickened on duct and small stones are the major n.

e jaundice so often accompanies thiasis as well as other diseases of liary tract, it requires detailed con- tion. The common causes of obstruc- undice which are relieved by surgery mmon duct calculi and tumors of the or the head of the pancreas. The im- ce of differentiating between these ctive lesions and hepatocellular jaun- annot be overemphasized. In the pres- of choledocholithiasis, it may be best lay operation until the jaundice has ed and the patient's condition im- . This is especially true if choledocho- is is complicated by pancreatitis. An essary operation must be avoided, and perative procedure is tolerated poorly e patient with nonsurgical jaundice.

past history consistent with gallbladder e strongly favors common duct stone; 0 of these patients will have had colic, t least one fourth will have had jaun- ne or more times prior to their pre- g illness. Therefore, intermittent or sing jaundice is of considerable diag- importance and indicates the presence ball-valve stone of Osler. The decrease esult from the passage of a stone into uodenum. While weight loss is more tive of malignancy, it is also seen in ts with common duct stones and usually results from nausea and food intolerance or fear of inducing pain. Although pruritus is supposedly a more prominent symptom of jaundice due to extrahepatic obstruction of the surgical type, it occurs frequently in patients with hepatitis.

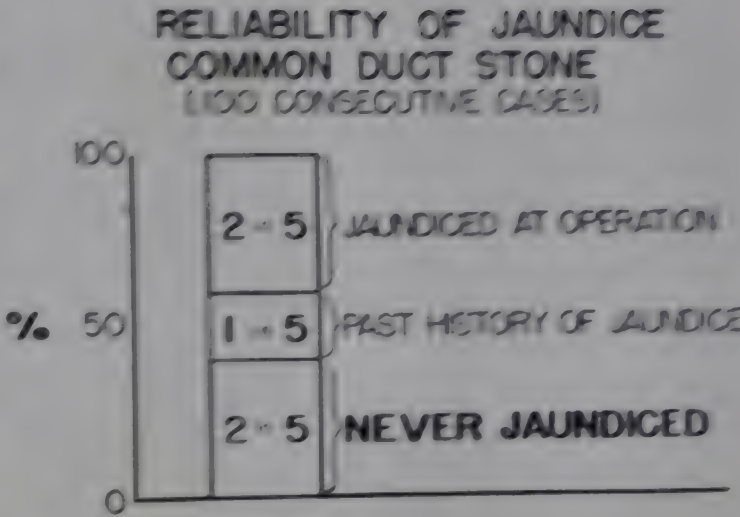


Fig. 231. In a recently reviewed series there was no history of jaundice in 35 per cent; there was a past history in 21 per cent; and at the time of operation only 44 per cent were jaundiced. It must be recognized that stones may occur in the common duct without accompanying jaundice and that other criteria than the presence of jaundice are necessary for common duct exploration in order to avoid overlooking any existing common duct stones.

The simultaneous finding of acute cholecystitis or acute pancreatitis in a jaundiced patient tends to confirm the diagnosis of common duct stone. It must be realized that although the cystic duct is blocked by a calculus during acute cholecystitis, stones may have escaped into the common duct prior to the obstruction. Furthermore, it emphasizes the necessity of determining the serum amylase if jaundice develops after a presumed attack of biliary colic, since, if the amylase is elevated, surgery should be delayed until the acute pancreatitis has subsided.

The development of jaundice immediately following gallbladder surgery strongly suggests injury to the common bile duct. An overlooked common duct stone or hepatitis from transfusion also must be considered in the early postoperative period. Neglected stone is the most probable cause in the late

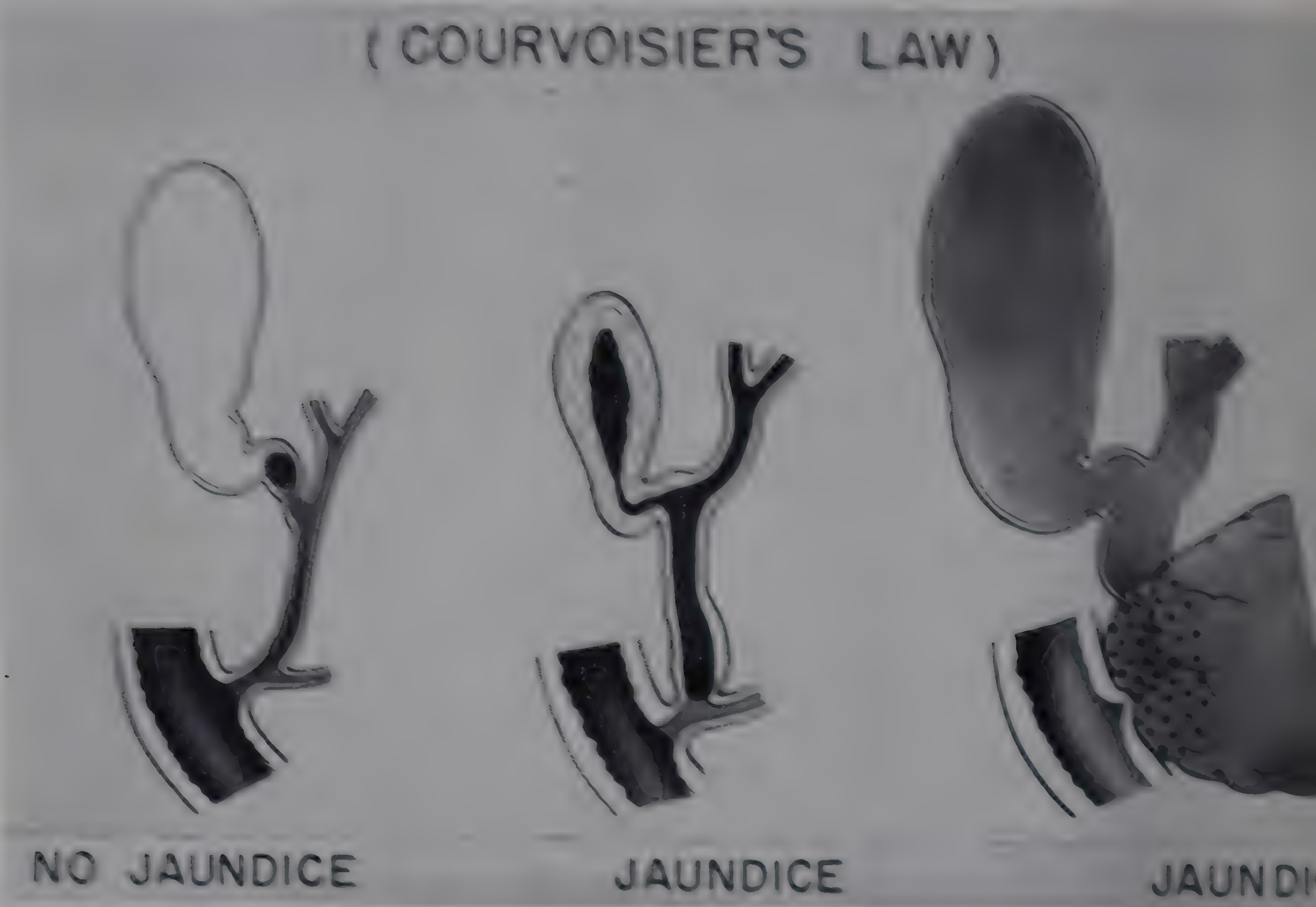


FIG. 232. The thick-walled and chronically infected gallbladder which is invariabl
associated with cholelithiasis cannot become distended in response to common duc
obstruction. Therefore, the patient with common duct stone may be tender in the righ
upper quadrant or epigastrium but almost never has an enlarged gallbladder.

postoperative period, especially if the gallbladder was drained only by cholecystostomy.

The history in obstruction by malignancy is not as helpful as in the patient with common duct stone. Many of these patients present themselves with bizarre and an occasional severe upper abdominal pain.

Physical Examination. This also may be of value in making the differential diagnosis. In the first place, an initial impression may be gained from the intensity of the jaundice, i.e., if the obstruction is complete, the patient's skin often a deep-greenish yellow as compared with the canary-yellow color associated with liver damage. Since the liver usually is enlarged and tender in the presence of jaundice, regardless of type, this finding contributes little to the differential diagnosis unless a hobnailed surface or definite metastatic nodules can be palpated. Evidence of either primary or recurrent malignancy of the gastro-intestinal tract su
metastasis in the region of the liver
In contrast with the palpable liver, the
ence of an enlarged spleen is of consid
importance and should serve as a d
signal to the surgeon. Congenital an
quired or secondary hemolytic anem
well as cirrhosis must be considered
calls for extensive hematologic investig
It should be remembered that many
patients have coexistent bile pigment s
both in the gallbladder and in the
hepatic bile ducts, which condition on
sion gives rise to a mixed type of ja
(hemolytic plus obstructive).[illegible] Rem
the stones without splenectomy may p
tate a hemolytic crisis manifest by ex
hemolysis, progressive and severe ane
spite of transfusions, mechanical plugg
the renal tubules with pigment, anur
death from uremia. Conversely, splen
alone may lead to the necessity of a s

ation to relieve biliary colic or
e jaundice.
ended, easily palpable gallbladder,
vidence of an acute inflammation
e presence of intense jaundice, usu-
cates a malignant obstruction of the
d of the common duct. In the ab-
jaundice, this same finding is indic-
a hydrops from a stone occluding
ic duct. As pointed out by Cour-
the thick-walled and chronically in-
allbladder, which invariably is asso-
with cholelithiasis, cannot become
d in response to common duct ob-
s (Fig. 232). The patient with com-
ct stone, therefore, may be tender in
t upper quadrant or epigastrium but
as an enlarged gallbladder. Finally,
ence of ascites or abnormal varicosi-
he abdominal wall suggests medical
han surgical jaundice.

ratory Tests. Having arrived at a
impression, and only then, the physi-
ay turn to the laboratory for con-
n of his working diagnosis. In gen-
e should place reliance on relatively
oratory tests insofar as differential
is is concerned, realizing, however,
re are others which have been quite
in evaluating the patient as a surgical
ernal examination of the stool and
ne is of considerable value. Gray
nd dark urine with negative tests for
ogen (Ehrlich benzaldehyde test)
omplete obstruction and, if persis-
or surgical intervention. Twenty-four
timates of urobilinogen excreted will
ired for interpretation if the obstruc-
incomplete. The stool also should be
ed for occult blood. A positive test
absence of increased bleeding tend-
suggests the presence of a malignant
in the ampulla. A test for bile in the
s of no diagnostic significance unless
in the presence of jaundice, and, in
stance, a diagnosis of congenital or
ed hemolytic anemia should be sus-
.

too much emphasis has been placed
atteries" or "profiles" of hepatic-
n tests to the neglect of a more care-
sideration of the results obtained from
l and more specific group of laboratory procedures. Therefore, the physician should familiarize himself with the interpretation and the limitations of each and should select those procedures most likely to indicate medical or surgical jaundice. At the outset it must be recognized that there are no specific tests for the differentiation of these two conditions. The icteric index or serum bilirubin serves equally well in estimating the severity and the progress of the jaundice. If an obstructive lesion is suspected, a fluctuating or decreasing icterus suggests common duct stone, while continued or progressive elevation, particularly if above 100, is strongly suggestive of malignant involvement of the ductal system. Therefore, determinations of the icteric index are made on alternate days during the acute phase of the disease, and, if the jaundice is found decreasing, operation is postponed until the patient's abnormal laboratory findings return to normal and the general condition is improved. The differential van den Bergh rarely influences the clinical impression except in patients with hemolytic jaundice where the indirect reaction is so consistently elevated.

An increased alkaline phosphatase to above 12 Bodansky units results in most instances from an obstruction of the biliary tree; however, it fails to differentiate extrahepatic from intrahepatic involvement. This is particularly important if one recalls that intrahepatic obstruction not infrequently occurs in progressive hepatocellular involvement and, if not considered, may result in unnecessary operation in a poor-risk patient. Furthermore, as liver disease worsens from continued and long-standing obstruction, the production of alkaline phosphatase by the liver cells may decrease to near normal levels and further confuse the diagnostic puzzle. These facts emphasize the importance of early and repeated laboratory evaluation.

A prolonged prothrombin time, which fails to respond to parenteral vitamin K, an increased cephalin flocculation[illegible] and a high thymol turbidity indicate cellular liver damage and, if progressive, offer considerable support to the diagnosis of medical jaundice. Once again, however, it should be realized that superimposed liver damage occurs from prolonged biliary obstruction, and under such circumstances useful but nondiagnostic results may be anticipated. Therefore, it follows that these studies must be made when the jaundiced patient is first seen by the physician and, if inconclusive, should be repeated in 7 to 10 days. Delay in obtaining these baseline measurements of liver function in the hope that the jaundice will subside nullifies, for the most part, their diagnostic value which might have suggested either medical or surgical jaundice.

More recently, the blood mucoprotein levels have been shown to be of value in jaundiced patients. The serum mucoprotein concentration is increased above normal in about 75 per cent of patients with malignancy and most all patients with infection. The findings in patients with jaundice are markedly different, depending upon the pathogenesis of the disease.[16] In those patients with hepatitis the mucoprotein concentration shows a marked reduction from normal and ranges from 16 to 35 mg. per cent. A similar reduction has been found in patients with cirrhosis. The patient with reported ascending cholangitis and intrahepatic obstruction was found also to have low levels. In extrahepatic obstructive jaundice regardless of etiology, the serum mucoprotein levels are almost always normal or elevated and range from 73 to 200 mg. per cent with an average of 107 mg. per cent.

Although the average rise from malignancy exceeds that for common duct stone, the highest values reported occurred in benign stricture and varied directly with the duration and the degree of obstruction.

The uniformly low findings in hepatocellular disease as compared with the consistent elevation seen in extrahepatic obstructions indicate that a knowledge of the serum mucoprotein concentration may be of value in differentiating medical from surgical jaundice when considered with other clinical and laboratory findings.

Additional laboratory procedures may be helpful in evaluating the risk of operation. The percentage of cholesterol esters is also an important and reliable indication of liver function. Although generally nondiagnostic as regards medical vs. surgical jaundice, their reduction to values below 50 per cent of the total cholesterol should be regarded as a poor prognostic sign when surgery i indicated. An altered or reversed albumin globulin ratio lends support to these observations and indicates the advisability of delaying operation. Anemia and lowered bloo volume are common findings in all forms o jaundice, and, although nonspecific in term of diagnosis, they should be corrected befor surgery.

Finally, a determination of the bloo amylase is also valuable, inasmuch as acut pancreatitis not infrequently is associate with common duct calculi, and, when this is present, surgical exploration should b delayed. Since the amylase value falls t nondiagnostic levels within 48 to 72 hours after the onset of the disease, its blood leve should be determined at the time the patien with jaundice is first examined. If the amylas is elevated, it is preferable to delay operation for a period of 3 or 4 days after i returns to normal.

Roentgenologic Examination. No jaundiced patient should be considered for operation without the benefit of an abdomina scout film and a complete gastro-intestina survey, regardless of how obvious the diagnosis may seem. Flat and upright films of th abdomen may show gallstones which, with history of biliary colic, help confirm a diagnosis of common duct stone. However, th clinician should not be lulled into a fals sense of security, since the demonstration o calculi does not rule out the possibility of nonsurgical cause of the jaundice. Evidenc of air or barium in the biliary tree or the gal bladder indicates the possibility of an internal biliary fistula which in the majority o cases has resulted from stones. The findin of an isolated and dilated loop of jejunum in the left upper quadrant or the presence o calcification in the region of the pancrea suggests coexistent acute or chronic pancreatitis and, in turn, surgical jaundice. On th other hand, an unrecognized splenic enlargement occurring secondary to hepatocellul disease may be demonstrated.

Although cholecystography has been considered inaccurate in the presence of jaundice, newer technics and contrast medi make possible the demonstration of gal stones in a surprising number of jaundice patients. It follows that if the jaundice decreasing, visualization of the gall- or the common duct should be d.

-intestinal roentgenograms can be lso in the differential diagnosis. ration of esophageal varices indi- probability of hepatic cirrhosis; a duodenal C-loop or anterior dis- nt of the stomach suggests acute or pancreatitis, while a partial obstruc- eformity of the second and the third of the duodenum results from in- by tumor of the pancreas or ter- ortion of the common duct.

nterior penetrating ulcer in the first econd portion of the duodenum and proximity to the common duct occa- produces sufficient inflammation and to result in obstructive jaundice and al picture quite similar to that of ic carcinoma. When this is sus- lateral and oblique views of the um, particularly when combined with mpt at visualization of the common fer considerable assistance in diag- determination of the 12-hour gastric n is also of value in suspected ulcer ns.

y, the finding of a primary tumor of tro-intestinal tract, particularly of the h or the colon, points to metastatic ment of either the extrahepatic or rahepatic biliary ducts.

PREOPERATIVE MANAGEMENT

prevention or the correction of prob- n nutrition assumes an importance rable with that of accurate diagnosis preoperative management of the jaun- atient. The wisdom of supplying ade- calories and protein to any patient ver disease has been shown clearly by and has an important bearing on the e of these patients who have sustained tantial loss of body weight. It follows, re, that the surgeon must concern f not only with the cause of the jaun- ut also should devote considerable oward estimating the protein and ca- eeds of the patient, allowing sufficient whenever possible for adequate nutri- replacement by mouth, by vein, or by the several methods of tube feeding, if such postoperative complications as retarded wound healing, sepsis, hepatic failure and the like are to be kept at a minimum.

All too often, attempts to meet these additional demands consist of a rather routine administration of 10 per cent glucose intravenously for a few days preoperatively with little or no attention to the patient's oral intake. This method offers little hope of providing sufficient calories to return the patient to a weight-gaining trend. Getting the patient to consume the required amount of food may be facilitated by individualizing the diet, so that it caters to the patient's taste.

Interval feeding of flavored milk beverages fortified with skimmed milk powder may be employed as a useful method of supplementation.

Unfortunately, anorexia or loss of appetite is seen commonly in the presence of jaundice or an external biliary fistula, and under these circumstances complete dependence on the oral route may be difficult. This is particularly true in the elderly patient who may have little or no incentive to eat. In such instances, augmentation of the daily oral intake may be realized either by intravenous infusion or by tube feeding. The giving of 1 or 2 liters of a 10 per cent dextrose with added protein hydrolysate is useful for intravenous supplementation. More recently, invert sugar and, finally, pure fructose solutions have become available for parenteral usage. Salt-poor liquid human-serum albumin is an excellent source of protein and is now available.

Carefully employed tube feeding also may be required and is particularly important for cardiac or other patients in whom intravenous therapy may be undesirable. Although it is an effective method of augmenting an otherwise inadequate dietary intake, the average patient finds it very disagreeable from irritation by the tube and must be made to understand the rationale for such feeding and that it will be discontinued as soon as an adequate diet can be eaten. It is well to start such feedings with homogenized milk. As much as 2½ quarts may be given during each 24-hour period, providing 84 Gm. of protein and a total of 1,680 calories. The milk base may be supplemented later with protein concentrations and starch hydrolysates as the tolerance increases. Inasmuch as fat is a rich source of calories and its absorption is frequently defective in the jaundiced patient, attempts should be made to hold this loss at a minimum. The addition of 1 Gm. of Tween-80[18] to each quart of feeding mixture or fresh bile "borrowed" from T-tube drainage of postoperative patients may bring fat absorption to near normal levels and increase the total calories available. Feedings are best given in amounts of approximately 200 cc. spaced between meals and during the evening hours to minimize any detrimental effect on the oral intake.

Vitamin requirements must also be considered if the patient is taking an inadequate diet, and supplements of vitamin B complex and vitamin C will be necessary. There is considerable evidence that thiamine as well as the other B-complex vitamins is involved in carbohydrate metabolism; therefore, liberal allowances are advisable when patients are receiving glucose intravenously. Opinions differ as to human requirements for vitamin C in disease; however, the ascorbic acid blood level falls nearly to zero with stress, and as much as 1 Gm. daily may be required. Although the routine use of vitamin K is not advocated for fear of increasing postoperative venous thrombosis, sufficient amounts (10 mg./day) must be supplied to ensure a prothrombin level above 50 per cent of normal, and it is best to defer operation until this minimal value is realized.[48] Finally, it should be remembered that intravenous injection of vitamins is wasteful unless added to a liter of solution and given slowly, since a large portion of the infused materials may be excreted in the urine.

Coexisting anemia and deficiencies in the blood and plasma volume must be corrected also. The availability of radioactive iodinated human serum albumin has permitted accurate and repeated studies of the blood and plasma volume in jaundiced patients and has increased the awareness of the frequency of blood and plasma deficiencies in these patients, hitherto unrecognized. Such studies have shown that nearly 3 out of 4 jaundiced patients have a deficit greater than 20 per cent of their calculated normal blood volume.[19] This finding, as already noted, is of particular importance in those patients with excessive weight loss. Not infrequently, 2 or 3 transfusions of whole blood are required to correct the deficit. Bed rest should be avoided if possible, and the patient will be more confident, and the surgeon more assured of a successful outcome, if the patient is able to be outside the hospital room.

It is always advisable to re-evaluate the jaundiced patient before setting a definite time for operation. Surgery should be delayed and actually is contraindicated if the history and the physical examination are indecisive for surgical jaundice due to a common duct stone, tumor, or stricture. Operation should be deferred if there is a history of recurrent transfusions or injections, exposure to drugs or poisons, or an enlarged spleen. Likewise, certain laboratory tests stand out as danger signals which must not be ignored.

To ensure a low morbidity and mortality rate the jaundiced patient requires more work and study in all aspects of diagnosis and treatment than almost any other type of patient. If a well-formulated plan is followed, it is possible to select with a high degree of accuracy those jaundiced patients most likely to be relieved by surgery. It should be remembered that neither age nor etiology is a contraindication to surgery in extrahepatic jaundice since the cause can be removed or palliation provided in a high percentage of cases.

PRINCIPLES AT SURGERY

The principles at surgery in the jaundiced patient are directed at relief of the jaundice, prevention of postoperative jaundice, and establishment of the type and the extent of liver damage.

Although all obstructing neoplasms cannot be removed, many may be by-passed so that the uncomfortable symptoms from intense jaundice and progressive liver damage are minimized. Prevention of postoperative jaundice can be attained by careful complete surgery and avoidance of injury to the common bile duct. Avoiding the use of plasma in favor of blood or serum albumin before and during the operative procedure will help decrease the incidence of postoperative jaundice due to hepatitis. In cases in which definite pathologic diagnosis cannot

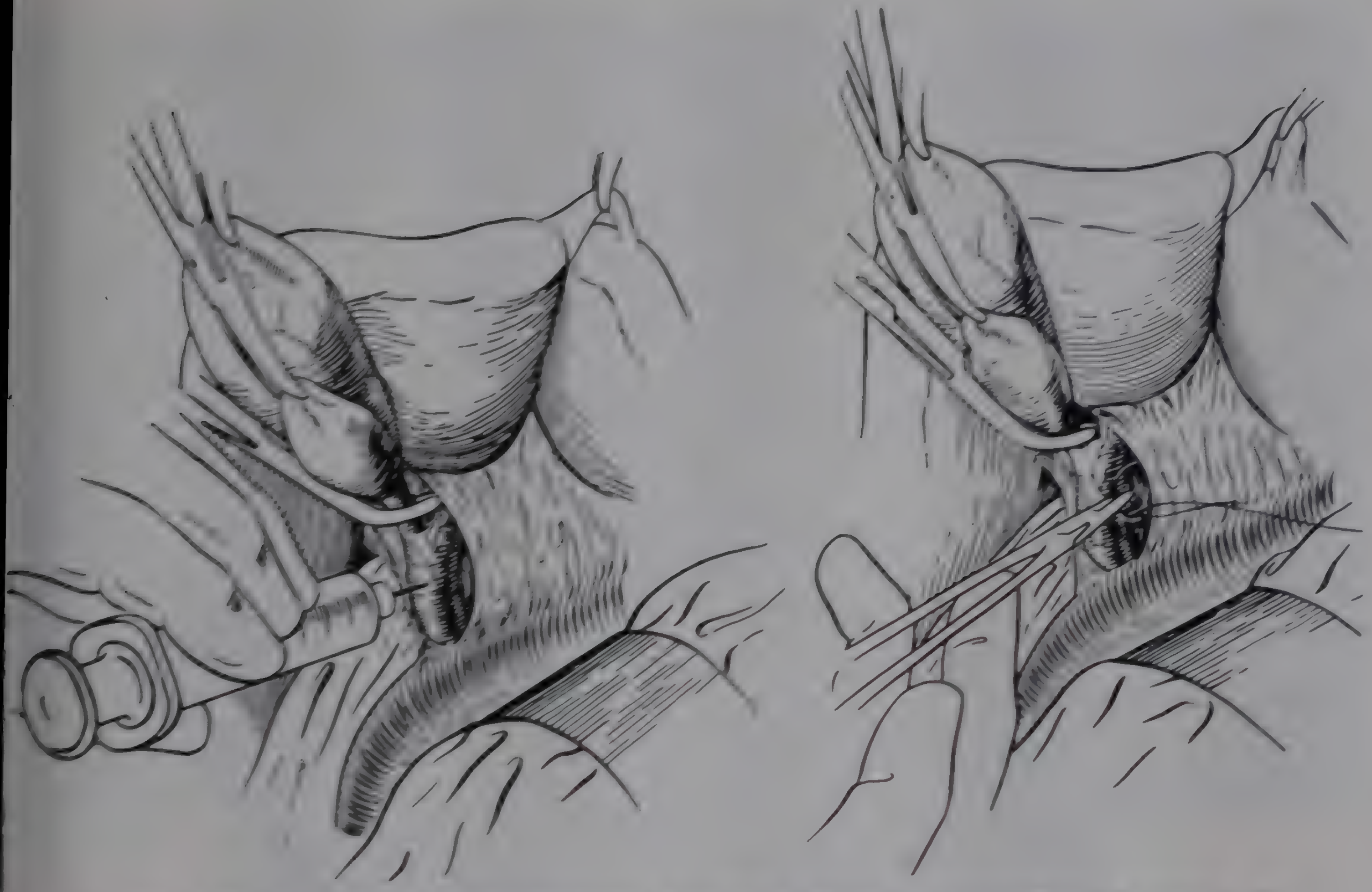


FIG. 233. Having extended the peritoneal incision in the hepatoduodenal ligament, the common duct is identified. Confirmation is obtained by aspiration of bile through a fine-gauge needle. Then traction sutures are placed at the site chosen for exploring the common duct.

established at surgery, it is imperative to tain a liver biopsy to aid in the diagnosis d the prognosis of the complicated case.

Very gratifying results are obtained if a mmon duct stone is recovered. The repair strictures, while not as uniformly success- l, is always worthwhile regardless of how any previous repairs have been attempted.

Although relatively few malignancies pro- icing obstructive jaundice can be extirpated rgically, the individual patient should be ven this opportunity.

CHOLEDOCHOSTOMY

Regardless of whether or not a common ıct stone is suspected, the size of the com- on duct and the thickness of its walls must e determined in every patient in whom the allbladder is removed. Therefore, the de- ils of exposing the junction of the cystic d the common hepatic ducts to form the ommon bile duct are included with the chnic of cholecystectomy.

Indications for Choledochostomy

HISTORY

1. Concurrent or previous jaundice
2. Frequent attacks of biliary colic
3. Pronounced involuntary vomiting
4. Recurrent chills and fever
5. Proved pancreatitis in the past
6. Previous cholecystectomy with recurrent symptoms, stricture or biliary fistula

OPERATIVE FINDINGS

1. Demonstrable common duct stones
   A. Palpation
   B. Cholangiography
2. Dilated common duct
3. Small stones in gallbladder with enlarged cystic duct
4. Induration in head of pancreas
5. Aspiration of light-colored bile with pigment precipitation
6. Thickened common duct with evidence of cholangitis

Operative Technic. If choledochostomy is indicated, the peritoneal incision in the hep-

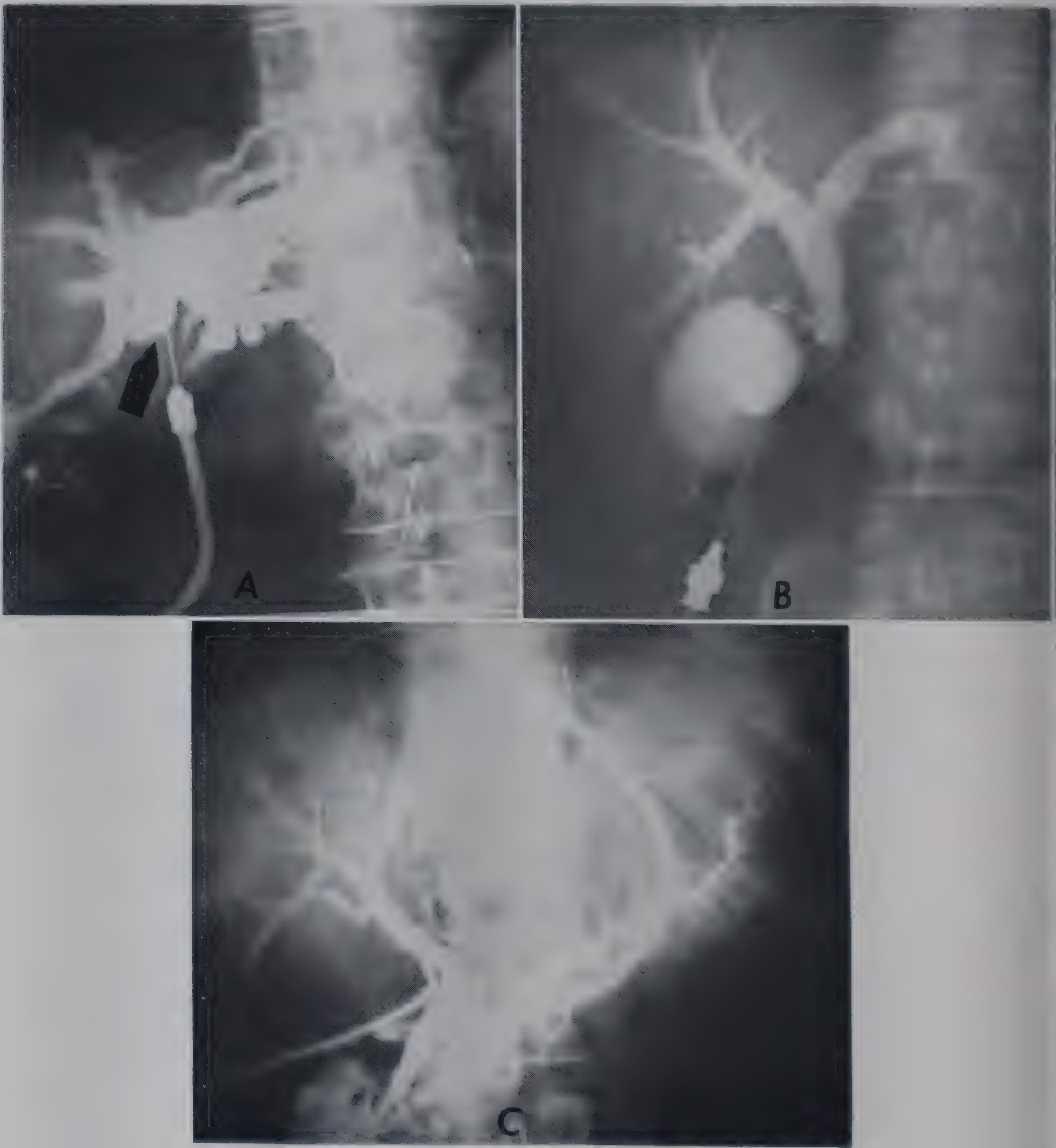


Fig. 234. Operative cholangiography. (A) A demonstration of site of malignant obstruction. (B) Benign stricture of the common duct resulting from operative injury at the time of subtotal resection for ulcer. (C) Common channel.

atoduodenal ligament is continued downward over the anterior surface of the common duct (Fig. 233). When this is done carefully, usually it is unnecessary to ligate any vessels. Although the common duct often can be identified by its position in the hepatoduodenal ligament or its attachment to the cystic duct, its color and the presence of a vein running along its anterior wall are also of value. The frequency of anatomic variations of the common bile duct, of the portal vein and other structures in this vital area makes further verification advisable. Final confirmation is obtained best by aspiration of bile through a fine-gauge needle. This helps to delineate the thickness and the consistency of the wall of the common duct and the color and the consistency of the bile. If cholangitis is suspected, the aspirated specimen is saved for bacterial culture and sensitivity studies.

In recent years, many surgeons have advocated operative cholangiography or visualization of the extrahepatic bile ducts by the injection of a radiopaque material into the common duct at this stage of the operation. The value of this procedure in demonstrating a common channel in those patients with an associated pancreatitis is commonly accepted (Fig. 234). Furthermore, it affords a method of determining the exact site of ductal involvement in the case of malignant obstruction and, in turn, the feasibility of choledochoenterostomy. Although it may be useful in avoiding a negative exploration or in the demonstration of a calculus which conceivably might have been overlooked, it should not be considered as a necessary prerequisite to exploration of the common duct since negative choledochostomy should not increase the general mortality.

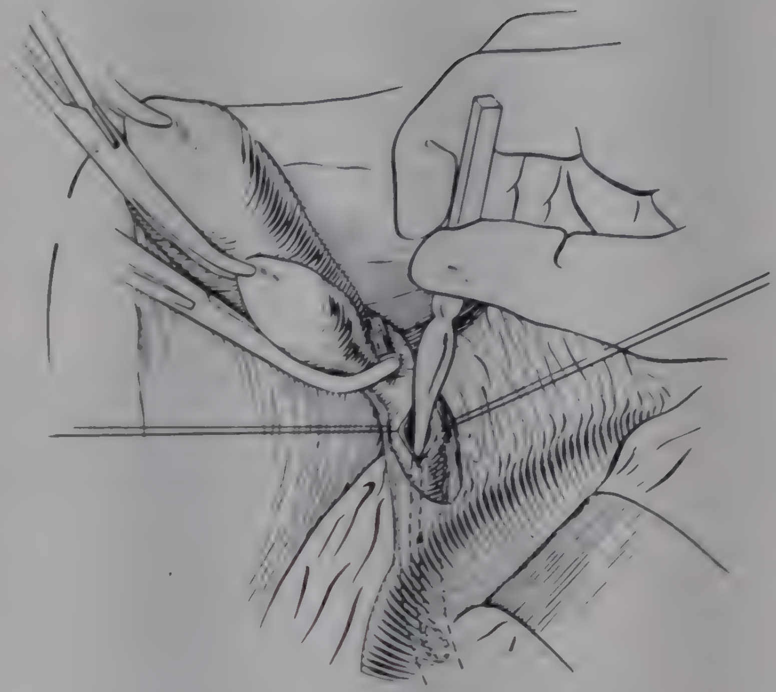


Fig. 235. A 1-centimeter incision is made parallel with the long axis of the duct between the traction sutures, and a careful and systematic exploration of the extrahepatic bile ducts is made with a small malleable scoop.

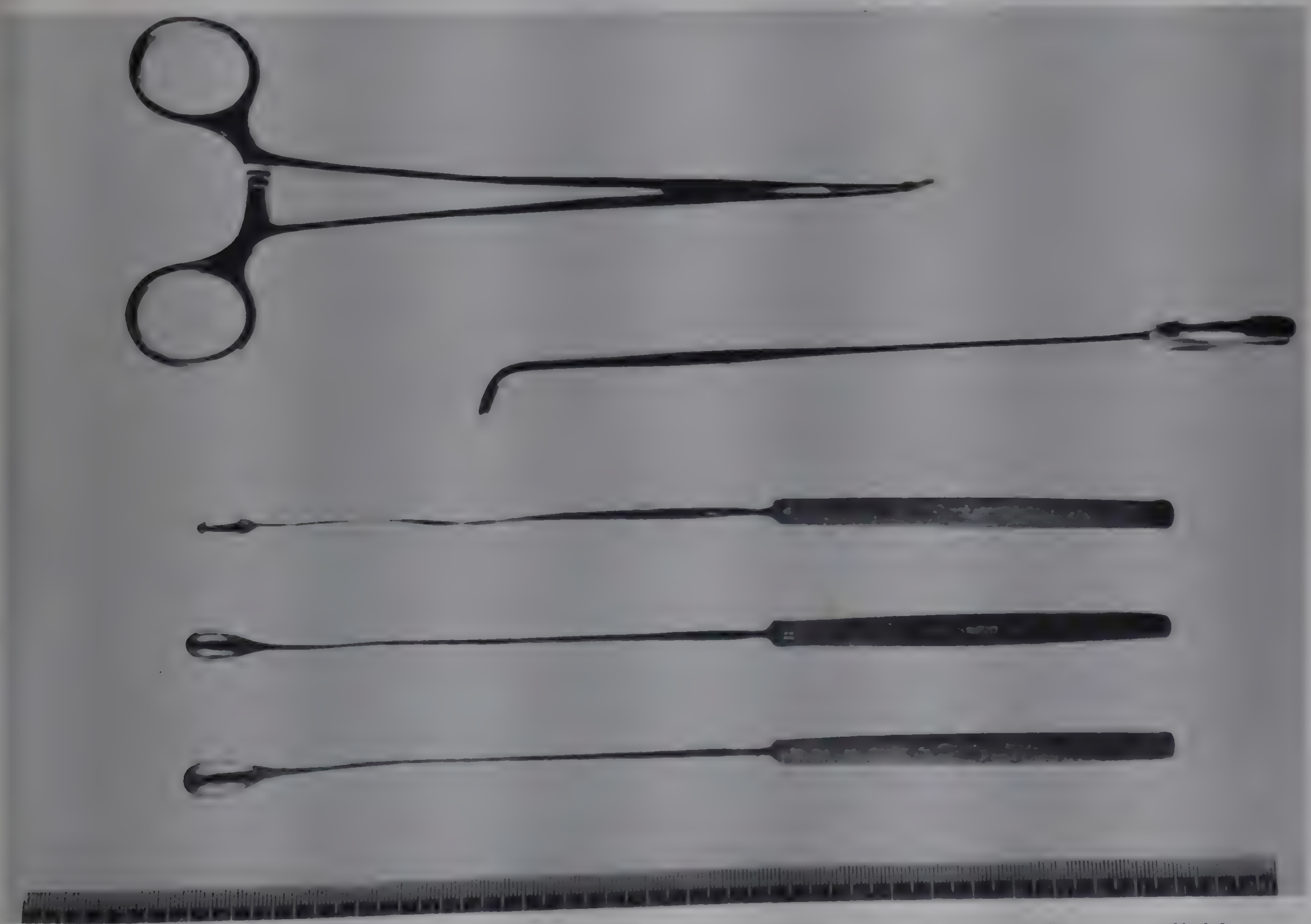


Fig. 236. The long-handled, malleable Cushing pituitary curettes which are available in 3 sizes are especially applicable to common duct exploration, inasmuch as their curvature can be adjusted easily to suit the individual patient's anatomy. The long narrow right-angle clamps are useful in dissection of the cystic and the common ducts.

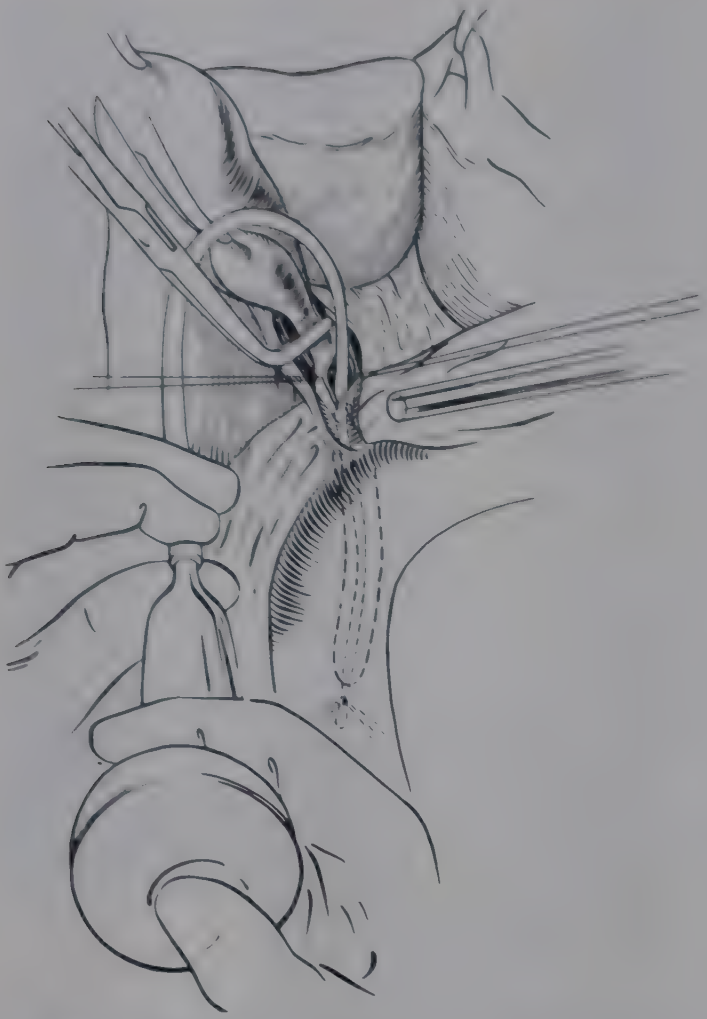


FIG. 237. It is advisable to irrigate the passages in an effort to dislodge and wash downward any overlooked stones in the hepatic ducts. Patency of the ampulla of Vater must be proved before closure.

The success of the exploration depends for the most part upon the availability of instruments which ensure the removal of all calculi with a minimum of trauma. Having obtained a satisfactory exposure of the common duct, 2 No. 0000 silk traction sutures on French needles are placed through its wall a few millimeters apart and just below the junction of the common and the cystic ducts. The operative site is walled off with moist Mikulicz pads. Using a small, sharp knife blade on a long handle, a 1-cm. incision is made parallel to the long axis of the duct between the traction sutures, avoiding, if possible, any vessels on the anterior wall (Fig. 235).

All bile that escapes from the opening is aspirated by means of a glass suction tube, taking care to note its color and consistency and the presence or the absence of small stones or "mud." After ascertaining that the opening is large enough to admit a small scoop without traumatizing or tearing the duct, a careful and systematic exploration of the extrahepatic bile ducts is made. The advisability of avoiding long straight instruments is realized quickly if it is considered that the lower third or pancreatic portion of the common duct lies behind or passes through the head of the pancreas and of necessity curves anteriorly before terminating in the duodenal papilla. Inasmuch as this curve varies in the individual patient, very malleable instruments are preferred (Fig. 236).

The patency of the common duct and papilla of Vater is determined best by directing a small flexible copper probe, such as a uterine sound, downward through the duodenal papilla and into the duodenum. The placing of the left index finger into the foramen of Winslow to offer counterresistance may facilitate this maneuver. Of more importance, the surgeon may detect a grating of metal against stone as the probe encounters and passes by nonobstructing calculi, and thereby find stones that otherwise might have been overlooked. Patency of the duodenal papilla does not rule out the presence of stone because a calculus may still be floating freely in the ampulla of Vater or be resting in a sacculation of the common duct. Therefore, a malleable scoop of small size is directed repeatedly into the ampullary region of the common duct, and any stones encountered are removed. The long-handled malleable Cushing pituitary curettes which are available in 3 sizes are especially applicable to this procedure inasmuch as their curvature can be adjusted easily to suit the individual patient's anatomy (Fig. 236). Furthermore, the size and the shape of the scoop itself permits easy exploration and recovery of calculi of almost any size with minimal chances of traumatizing the delicate duct tissue. On occasion, stones impacted in a common duct diverticulum or lying to one side of the ampulla of Vater may be fixed between the left thumb and the forefinger, fragmented by the metal scoop and removed piecemeal or by irrigation. Although the majority of calculi are recovered from the lower end of the common duct, it is not unusual to find one or more small stones in the common hepatic duct or in the large intrahepatic bile ducts. For this reason, the small scoops should be directed upward into both the right and the left hepatic ducts as well as downward in the search for stones. The importance of a careful and systematic exploration of this region was substantiated a number of years ago by autopsy findings in patients who had expired a few days following choledochostomy; in spite of a most thorough exploration, small calculi had been overlooked in a distressingly high percentage of cases.[9] Therefore, it is advisable to irrigate these passages in an effort

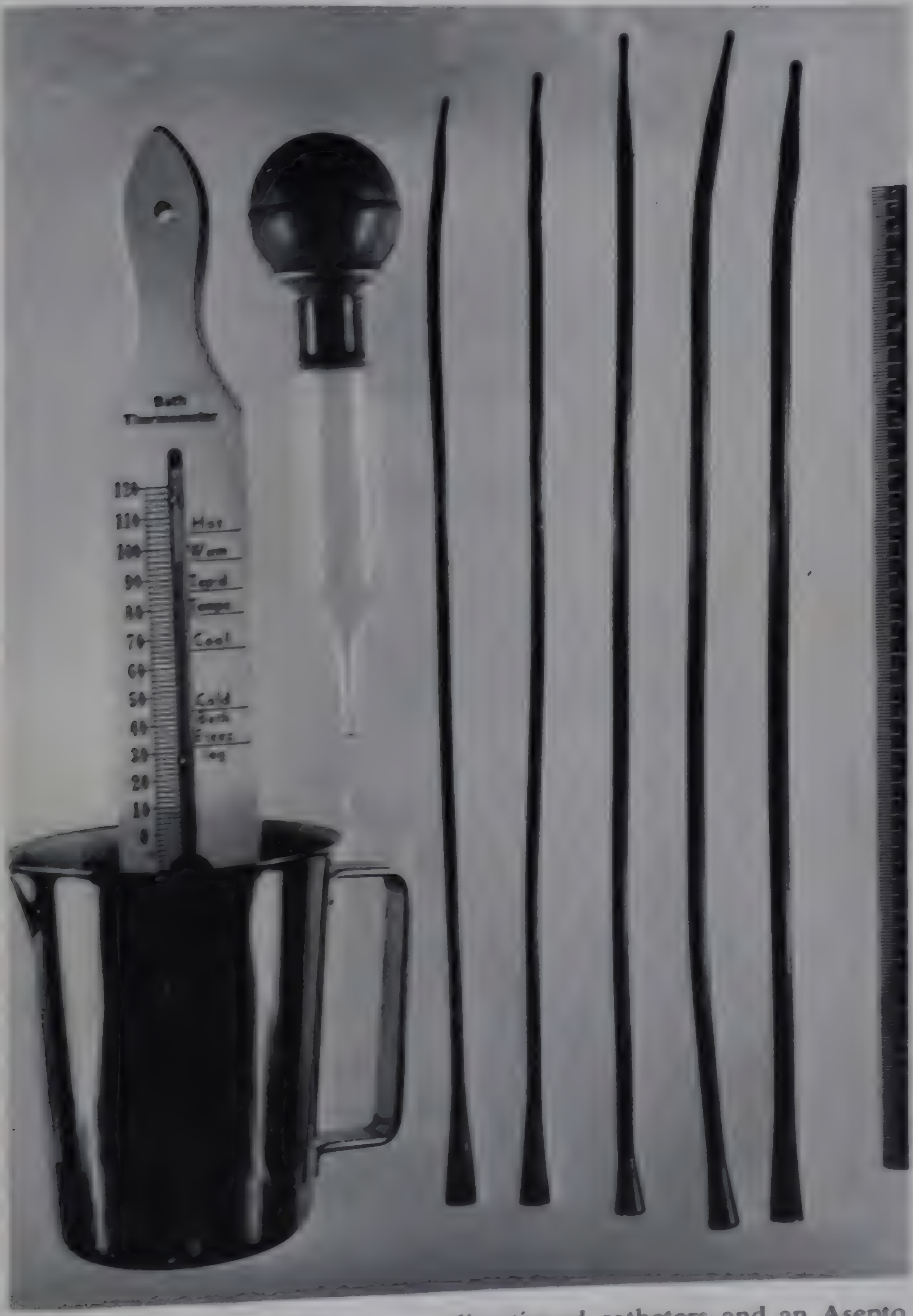


FIG. 238. French, silk-woven, olive-tipped catheters and an Asepto syringe are used to inject warm saline into the ductal system. Under no circumstances should saline be injected without first determining its exact temperature by a thermometer reading. The temperature should not exceed 110° F.

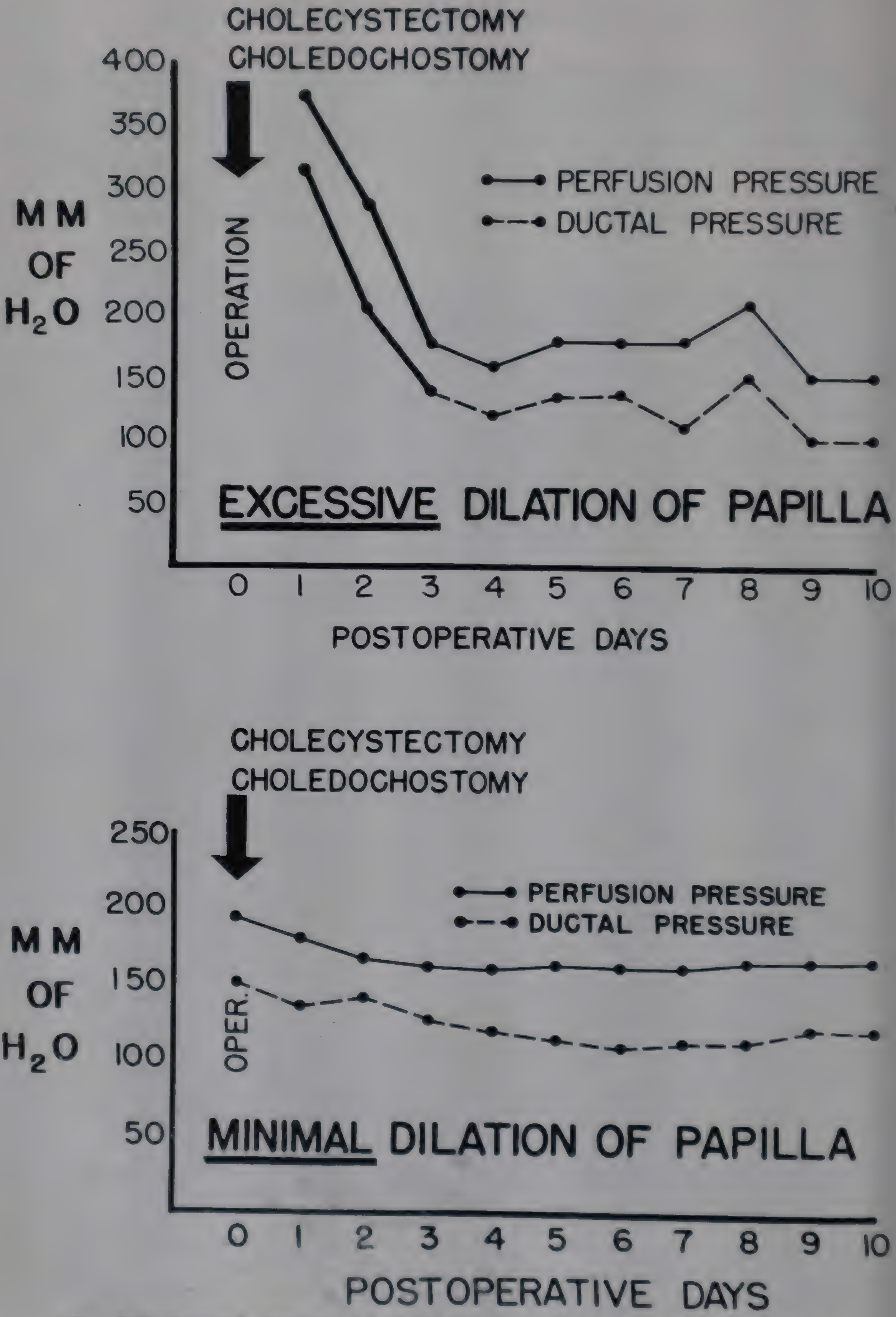


FIG. 239. Forceful dilatation invariably increases the postoperative perfusion and ductal pressures to twice the normal values and actually may preclude the passage of calculi. In addition, subsequent scarring with narrowing of the opening may occur.

to dislodge and wash downward any overlooked stones in the hepatic ducts (Fig. 237). For this purpose, a No. 10 or 12 French, silk-woven, olive-tipped catheter is inserted into the common duct and directed toward the liver and into the right hepatic duct; using an Asepto syringe, warm saline less than 110° F. is injected as the catheter is withdrawn. The procedure is repeated with the tip of the catheter in the left hepatic duct. Under no circumstances should saline be injected without first determining its exact temperature by a thermometer reading (Fig. 238). The actual presence of a thermometer in the saline container serves as a constant reminder to the nurse that temperature is important, and the surgeon is less likely accidentally to inject solutions sufficiently warm to injure the duct tissue. The two openings in the woven catheters are so placed that forceful injection of saline sets up a whirling current useful in the washing of debris or dislodging any remaining calculi. Fluid that escapes around the catheter is removed by continuous suction. Then the flexible catheter is directed downward past the sphincter of Oddi and into the duodenum. In most instances, a sudden increase in resistance is encountered as the catheter passes through the papilla of Vater. Saline is injected slowly, and if the olive-tip is within the lumen of the duodenum, the latter will distend with fluid and offers an ideal method for determining the patency of the papilla of Vater. As the catheter is withdrawn, normal saline can be injected again to float any debris or dislodge any calculi in the common duct. However, the possibility of inducing pancreatitis by this maneuver cannot be overlooked.[50] For this reason, there is a tendency toward less and less manipulation and irrigation within or close to the ampulla.

The problem of whether or not to dilate the papilla of Vater after its patency is established has been debated for a long time.[51] Those in favor contend that dilatation permits better drainage of bile and the escape of overlooked common duct stones. Arguments against dilatation of the papilla of Vater include the observation that forceful dilatation invariably increases the postoperative perfusion and ductal pressures to twice the normal values and actually may preclude the passage of calculi. Furthermore, experimental dilatation in animals has shown similar increase in pressures and, in addition, subsequent scarring with narrowing of the opening (Fig. 239). For these reasons, the patency of the papilla of Vater should be determined gently, and under no circumstances should an effort be made to dilate it forcibly. Therefore, rigid dilators or metal bougies should be avoided inasmuch as flexible silk-woven catheters are quite satisfactory for determining patency of the papilla without the danger of stretching or tearing the delicate mucosa or the sphincter muscle. These catheters are available in graded sizes (F-10 through F-18) (Fig. 238). The small bulbous tip expedites passage through the papilla, and the graduated increase in size

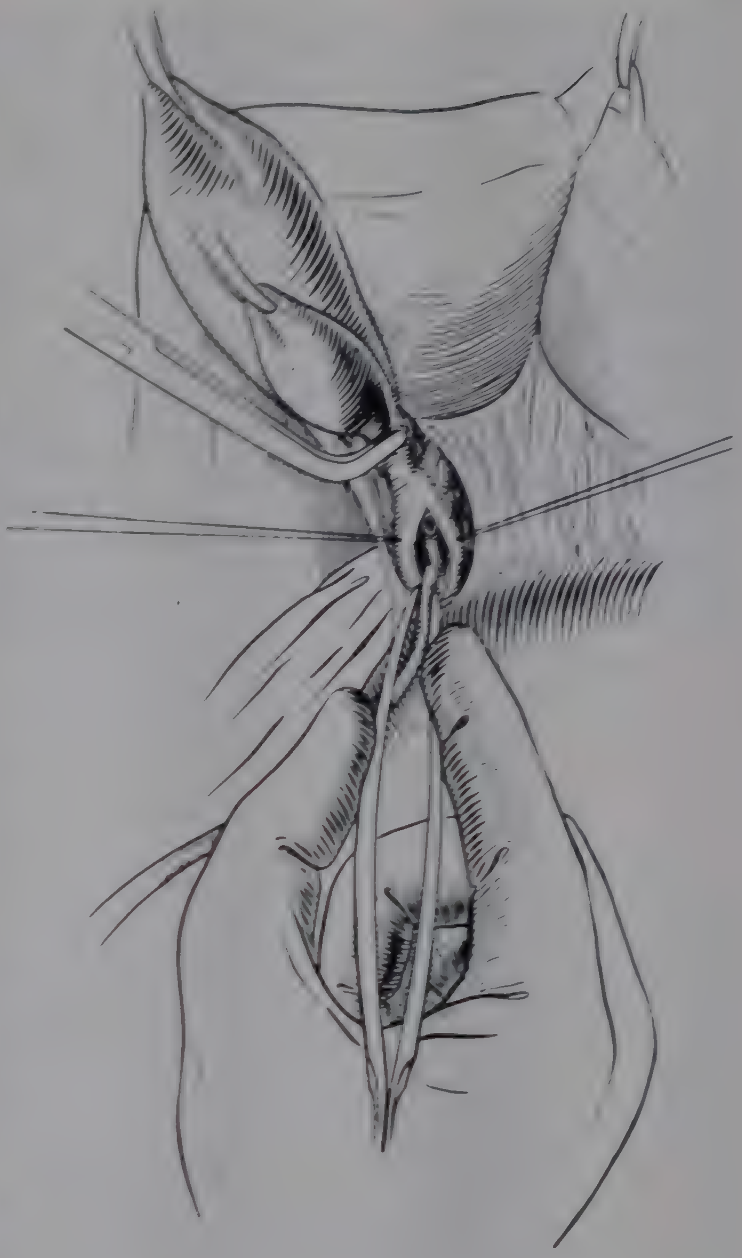


FIG. 240. A short-armed T-tube (No. 16 or 18 French) is inserted in the common duct.

of the catheter from the tip upward ensures gentle dilatation.

After manipulation of the common duct has been completed, a small open-end common duct catheter or short-armed T-tube (No. 16 or 18 French) is inserted in the common duct (Fig. 240). If a catheter is used a No. 0000 silk suture is placed in one side of the opening in the common duct and 2 to 3 cm. from the tip of the cathet
hold it in proper position. The suture sl
include only a few millimeters of duct t
and deliberately is tied very tightly to c
early sloughing. If a T-tube is used, a w
is excised opposite the main stem to f
tate removal, and the ends are cut
(Fig. 241) in an oblique fashion to r
mize trauma to the common duct wh

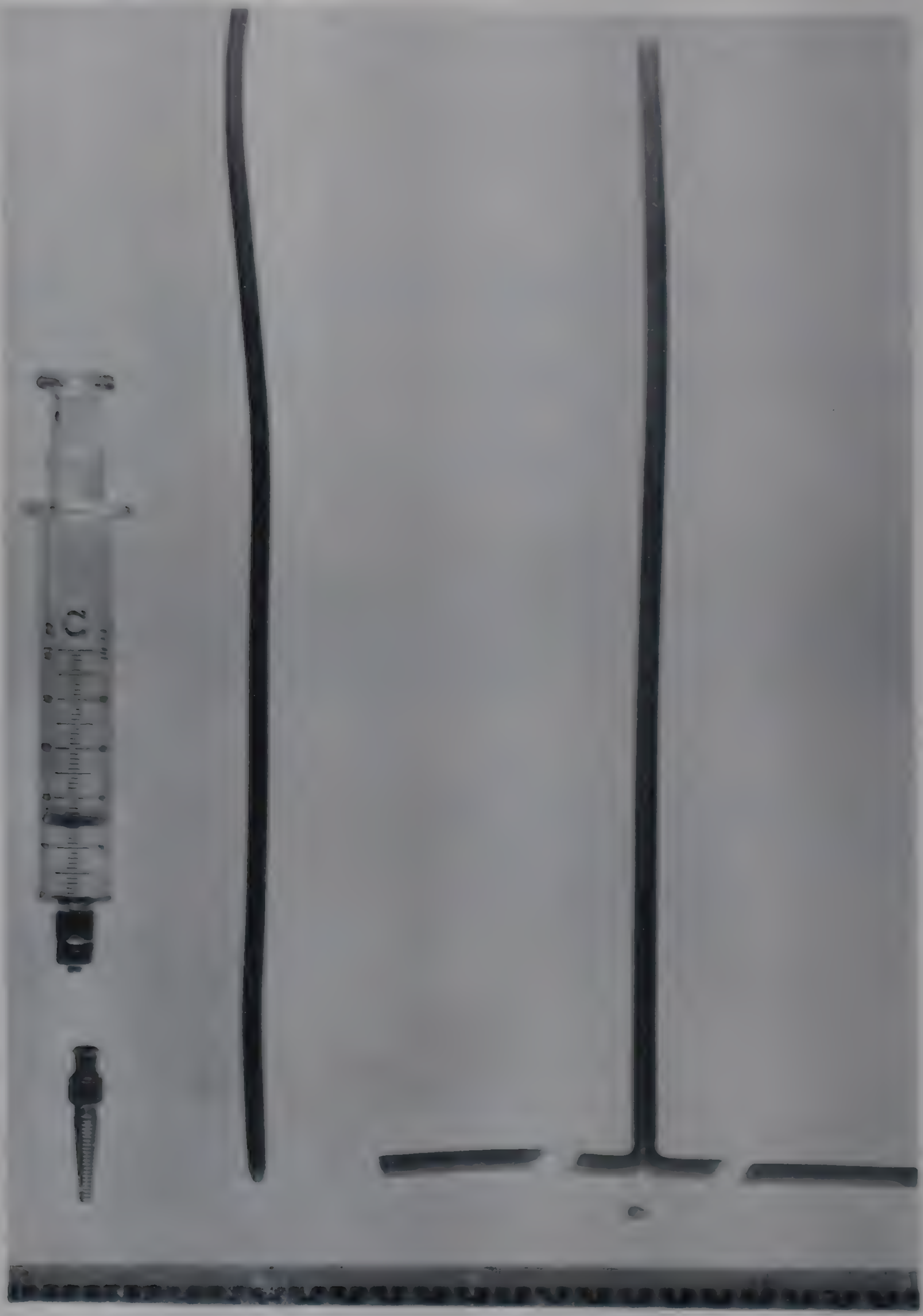
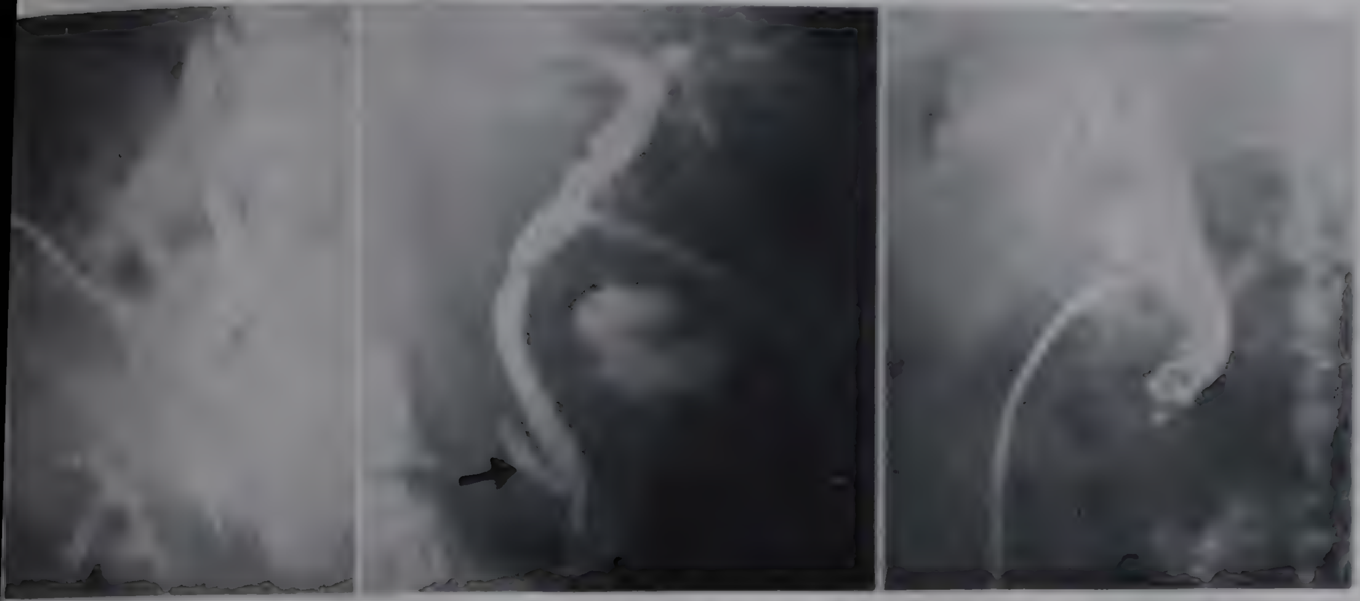


FIG. 241. T-tube or straight catheter for common duct drainage. If a T-tube is used, a wedge is excised opposite the main stem to facilitate removal, and the ends are cut short in an oblique fashion to minimize trauma to the common duct when it is removed.



c. 242. Postoperative cholangiograms. (A) Blood clot in dilated duct simulating
looked stone. (B) Common channel. (C) Overlooked stones with long-armed T-tube
h prevents washing out by irrigation.

ed. Long-arm T-tubes are not used
, since the upper long arm may ob-
e right or the left hepatic duct and
persistent jaundice and liver dam-
e lower arm may obstruct the pan-
luct if it extends down to or through
pilla and produce a pancreatitis;
more trauma is produced during re-
of the longer-armed tube. Further-
has been noted that any overlooked
demonstrated by postoperative chol-
aphy cannot be washed out by irri-
the lower arm of the T-tube extends
the stones (Fig. 242).
pening about the catheter or T-tube
secureley with No. 0000 silk sutures
ch needles, and the suture line is
y injecting saline through the cath-
Penrose drain is placed down to the
of Winslow, and the catheter and
n are brought out through a stab
at least 3 or 4 inches lateral to the
to avoid acute angulation and ob-
of the catheter and possible con-
on of the wound with bile. The
um and the fascia are grasped by
clamps and pulled toward the mid-
le the stab wound is made to ensure
distance between the drainage
and the peritoneal closure.
re radical approach has to be fol-
the surgeon is unable to dislodge a
from the lower portion of the common duct or establish patency of the papilla of Vater. Under these circumstances, the second portion of the duodenum is mobilized by incising its lateral peritoneal attachment and sweeping the duodenum medially by gentle finger dissection (Kocher maneuver). Occasionally, this will expose the retroduodenal portion of the common duct, permitting more direct palpation which, with the aid of a scoop in the common duct, enables the surgeon to dislodge or fragment the calculus. In rare instances, it may be necessary to incise the common duct directly over the stone, and, having assured oneself that no additional stones are present, the lower incision is closed, and a T-tube or a soft-rubber catheter is inserted through the initial opening to decompress the common duct during the early postoperative period. Should these procedures prove to be unsuccessful, the anterior duodenal wall is incised, and the papilla of Vater is examined under direct vision. This transduodenal exposure of the distal common duct permits removal of stones impacted in the ampulla, and of equal importance may establish a diagnosis of a previously unsuspected pancreatic or ductal carcinoma.

The proper site to open the duodenum may be established by exerting slight pressure on a probe in the common duct and palpating its tip in the region of the papilla through the anterior duodenal wall. The field is walled off completely by gauze sponges, and suction must be available to avoid contamination by bile and pancreatic juice. The duodenum is stretched taut with Babcock forceps or traction sutures of silk and a 3 to 4 cm. incision is made over the papilla and parallel to the long axis of the bowel. Gauze sponges with long silk sutures attached are inserted proximally and distally in the duodenum to prevent soiling. If a calculus can be felt in the ampulla, it still may be expressed by palpation, or a small incision in the papilla of Vater may be required. The general direction of the duct is determined again by means of a probe, and an incision is made directly parallel to it so that the calculus can be removed manually or with a fenestrated stone forcep. Gentle pressure on the probe in the common duct may aid delivery of a large stone. Bleeding vessels in the papilla are controlled with fine silk sutures, and no attempt is made to reconstruct the papilla. Following removal of the calculus, scooping and irrigation are repeated from above to make certain that no overlooked stones remain. The protecting sponges in the duodenum are removed, and the opening in the bowel wall is closed either transversely or longitudinally, using 2 layers of interrupted nonabsorbable sutures. This closure must be water-tight and secure to avoid the distressing complication of a duodenal fistula. A silk-woven catheter is reintroduced into the common duct, and the duodenum is distended with saline to make certain there is no leakage. The common duct is drained with a T-tube or a catheter. One or two Penrose drains are inserted down to the foramen of Winslow; however, care is taken that the ends do not lie on the duodenal suture line.

One of the most frustrating experiences of the abdominal surgeon is to operate on a deeply jaundiced patient with all the criteria of an obstruction of the extrahepatic bile ducts, only to find no evidence of stones, tumor or stricture. The jaundice in these cases proves for the most part to be of the intrahepatic obstructive type or has resulted from severe hepatocellular disease and represents a mistaken preoperative diagnosis. Two factors stand out as important causes for this error in the jaundiced patient,

namely, an x-ray diagnosis of assoc
gallstones and laboratory evidence sug
ing but not conclusive for obstruct
Evidence of severe liver damage is pre
in most instances and raises the question
to whether sufficient time has been allo
to re-evaluate the laboratory evidence.
though the jaundiced patient should no
"studied to death" before operation,
it is desirable to delay surgery until the d
nosis of surgical jaundice is more cer

When during operation no evidence
stones, tumor or jaundice has been fo
patency of the papilla of Vater always m
be assured before closure, and every me
ure possible must be taken to establish
exact diagnosis. Operative cholangiogra
is advisable in these questionable ca
since the best opportunity for diagnosis
treatment is available at the initial op
tion. An adequate liver biopsy is of e
importance so as to determine the type
the extent of liver disease and may as
the physician in planning subsequent th
apy or in giving a more accurate progno

If the gallbladder is thin-walled, emp
easily and contains no stones, and the co
mon bile duct is of small size, the bili
tree is studied best by the injection of c
trast media through the gallbladder or
cystic duct, thus avoiding choledochosto
in a poor-risk patient with severe liver
ease. On the other hand, if the comm
duct is dilated, the surgeon should sus
malignancy, pancreatitis, or an isola
common duct stone. These indicate expl
tion of the common duct even in the
sence of a palpable mass. If no obstruct
is found, a T-tube or a common duct cat
ter is inserted, and cholangiography is
complished by means of the inlying cathe
Primary closure of the common duct
been suggested in selected patients wit
evidence of stones or obstruction. Howe
the trauma of instrumentation may prod
sufficient edema of the sphincter of Odd
result in its temporary occlusion. The
creased biliary pressure then forces d
age of bile through the suture line
subphrenic or subhepatic collections of b
or a bile peritonitis. For this reason,
catheter drainage seems to be logical

ollowing exploration of the common

Postoperative Care

same general postoperative meas-
pply to patients with a common duct
ation as outlined for those who had
-cholecystectomy. However, as a rule,
patients carry a slightly higher mor-
and mortality expectancy. The un-
d effects of jaundice on the liver, the
ility of pancreatitis or anuria and the
sed caloric intake before and after
ion are some of the factors to be con-
d in postoperative care.

possibility of postoperative pancre-
must be kept constantly in mind.
amylase levels are determined on the
ostoperative day and at any time the
t's progress is unsatisfactory without
s explanation. The Levin tube is re-
d customarily in 24 hours to relieve
on and accumulation of secretions in
popharynx, and the oral intake is in-
d according to the patient's tolerance.
and clear liquids usually are accepted
second or the third day; however, it
d be pointed out that most patients
a poor appetite as long as bile is lost
outside. For this reason supplemen-
nfusions may be necessary for a longer
d than usual.

rubber drain is advanced on the first
following operation and usually re-
d at 48 hours. Once the patient is
latory, the drainage bottle may be
ced with a rubber glove which is
d dependently in a pocket. The drain-
ottle may be elevated gradually to the
of the patient or higher after the fifth
o decrease the amount of external bile
age. If a T-tube has been used, it may
amped off during the day and allowed
ain at night.

**easurement of Common Duct Perfusion
ures.** On the sixth or the seventh post-
ative day common duct perfusion pres-
are measured. Equipment required
des a water manometer, a 250-cc. bot-
sterile normal saline, a standard infu-
set and a screw clamp. The saline bottle
ached to one limb of the glass T at the
m of the manometer by means of rubber tubing. Then saline is used to fill all the tubing and the water manometer up to a pressure of 100 mm. of water. All bubbles are eliminated. The bottom of the water manometer is allowed to hang free at the level of the common bile duct. The remaining limb of the manometer is connected to the common duct tube, making sure that no bubbles are present and that the water in the manometer is allowed to seek a level (5 to 10 minutes). This is the intraductal pressure which normally is 80 to 100 mm. of water.

The screw clamp is opened so that saline may drip through the system at a slow but steady rate. The water in the manometer will rise until the sphincter pressure is overcome, and at this point the water column will drop. The pressure required to open the sphincter is called the *sphincter opening pressure* and normally is 150 to 200 mm. of water. If the sphincter opening pressure is increased greatly, it is not advisable to remove the common duct tube.

When the sphincter opens, the saline infusion is slowed until it barely drips. The water column now will seek another level somewhere between the intraductal pressure and the opening pressure. This is called the *perfusion pressure* and represents the pressure required to keep the sphincter open once the initial opening pressure has been overcome. Determinations may be repeated by stopping the saline drip and allowing the ductal system to return to equilibrium.

Having completed these measurements, a cholangiogram is performed to be certain that there are no residual calculi or areas of obstruction. One of the water-soluble urographic media is quite satisfactory for visualization. High concentrations should be avoided because of the irritating effect on the ductal system. Should the patient develop abdominal symptoms after the cholangiography, pancreatitis should be suspected, blood amylase levels determined, and the T-tube undisturbed until the patient is symptom free. If no discomfort is experienced by the patient, and if the cholangiograms and the perfusion pressures are normal, the catheter is removed 24 hours later by continuous gentle traction, and the patient can be discharged after drainage ceases. If there is prolonged or excessive bile drainage while the tube is in place, collected bile may be readministered by mouth or nasogastric tube to increase the appetite and fat absorption. Excessive bile drainage from the T-tube or sinus tract indicates persistent obstructions due to: prolonged spasm and edema of the sphincter of Oddi, an overlooked common duct stone, failure to identify a common duct stricture or injury to the ductal system at the time of surgery.

ACUTE PANCREATITIS

INCIDENCE

Acute pancreatitis is a more common complication of gallbladder disease than is generally realized.

ETIOLOGY

Although numerous theories of its etiology have been advanced, the termination of the pancreatic duct proximal to the ampulla of Vater, leading to a "common channel" for pancreatic and biliary secretions and the presence of gallstones are noted in a significant percentage of cases. In these patients, impaction of a gallstone in the ampulla or spasm of the sphincter of Oddi secondary to gallbladder disease favors the reflux of bile into the pancreatic duct which presumably leads to pancreatitis. Gallstones seem to be a particularly important factor, inasmuch as they may be demonstrated either by operation or cholecystography in nearly one half of the cases of acute pancreatitis.[39]

DIAGNOSIS

For this reason it is advisable to determine the serum amylase levels in all acute abdominal episodes suspected of originating in the biliary tract. Although an elevated serum amylase is diagnostic, these levels tend to fall to normal within 24 to 48 hours following the onset of the acute process. In those instances where pancreatitis is suspected but the patient is seen relatively late in the course of the disease, it may be helpful to study the amylase values on the peritoneal fluid obtained by simple mid-line peritoneal tap.

Technic for Mid-line Peritoneal Tap. This procedure is performed much as a routine paracentesis with the patient in a semisitting position. Using local anesthesia a blunt-tipped, No. 20 spinal needle is inserted into the peritoneal cavity near the mid-line below the level of the umbilicus. Then the obturator is removed, and fluid is aspirated into a syringe. Analysis of the peritoneal fluid for bile by the Gmelin method and titration of total acidity, as well as determination of the amylase value, is of value in the diagnosis of perforated peptic ulcer and a ruptured gallbladder.

Laboratory Tests. The routine blood count and urinalysis in suspected acute pancreatitis demonstrate a leukocytosis and occasionally glycosuria. Testing the urine for amylase and glucose may be worthwhile. Determination of the serum bilirubin or icteric index is important when the possibility of an obstructing common bile duct calculus is suspected. The serum calcium level may be reduced and is inversely proportional to the severity of the disease; values below 7 mg. per cent indicate a poor prognosis.

CONSERVATIVE MANAGEMENT

Blood-volume determinations have shown that considerable plasma and red cells and. not infrequently, albumin are lost from the circulation in patients with pancreatitis. Whole blood or one of the plasma substitutes may be required to prevent or control shock. Human serum albumin, originally recommended for its antitryptic effect, is definitely worthwhile, although its benefits most likely result from its maintenance of plasma volume at more normal levels.

The use of an indwelling gastric tube with continuous suction controls vomiting and, of more importance, decreases the production of secretin and pancreozymin and in turn pancreatic secretion by minimizing the entrance of acid gastric juice into the duodenum.

Further decrease in the gastric acidity is obtained by the use of vagal blocking drugs, either atropine (0.4 mg. every 4 hours) or probanthine (50 mg. every 6 hours). These vagal blocking drugs also act directly to diminish the nervous phase of pancreatic secretion.

Other details of the conservative management include bed rest and, of course, nothng by mouth. Fluid and electrolyte balance are maintained by the intravenous route. Frequent, periodic, abdominal examinations and checks on the vital signs must be done; and repeated determinations of the significant laboratory tests (blood count, amylase, calcium, electrolytes) at intervals are helpful, particularly in patients whose progress is unsatisfactory. Appropriate measures for shock should be carried out prophylactically. From 25 to 50 gm. of human serum albumin may be needed daily for several days to maintain the plasma volume within normal limits.[14] Should anemia develop, whole blood should be used. Prophylactic therapy against the development of infection and peritonitis should be instituted by use of appropriate antibiotics. If diabetes mellitus with hyperglycemia develops, insulin may be required. It should be remembered, however, that injection of insulin is the basis for the Hollander test for completeness of vagus section, and if hypoglycemia results, strong vagus stimulation results. Therefore, the giving of insulin should be done with extreme caution. In severe cases of acute pancreatitis, the serum calcium is frequently lowered, and in these instances 1 gm. of calcium gluconate should be given daily by the intravenous route.

It is not uncommon to find a modest elevation in the serum amylase without clinical signs of pancreatitis following cholangiograms or perfusion pressure studies made prior to removing a common bile duct catheter. Other than this form of the disease, pancreatitis developing in the postoperative period following biliary tract surgery is a severe and ominous disease and calls for all the measures described above. The prevention and the management of this complication are discussed in detail under choledochostomy.

SYMPTOMS AFTER CHOLECYSTECTOMY

The finding of an occasional patient who complains of recurrent symptoms following cholecystectomy should not condemn the surgical management of gallbladder disease. Usually the trouble can be ascribed to one or more of 4 fundamental reasons:

1. Incorrect preoperative diagnosis. This group includes failure to recognize concomitant pathology as the prime cause of the patient's symptoms and, finally, the poor selection of patients for surgery. Cholecystectomy performed in borderline cases or where disease does not exist carries an endless chain of distressing digestive symptoms. Attention to the principles already outlined will help reduce this group to a minimum.
2. Incomplete surgery. This includes failure to completely remove the gallbladder or the cystic duct or overlooking a common duct stone.
3. Complications resulting directly from the operation, including injury to the duct system.
4. Residual nonoperable disease of the biliary tract, including "biliary dyskinesia."

The patient who has had a surgical drainage and removal of stones without subsequent removal of the gallbladder is very likely to have a recurrence of symptoms. Since the patient is frequently not well informed as to what was done at this primary surgery, it is important to obtain an accurate description of any previous operation. A certain number of these patients have the mistaken impression that cholecystectomy was accomplished when actually the procedure was limited to cholecystostomy. In the past, too many patients have been denied benefits of cholecystectomy in lieu of anticipated difficulties at the time of reoperation. Complete removal of the gallbladder usually relieves the symptoms.

Remnant of Cystic Duct

A remnant of the cystic duct overlooked at the time of cholecystectomy has been recognized as the cause of postcholecystectomy symptoms and has received considerable attention in recent years.[42] The mechanism of symptoms is probably the same as that for symptoms arising in a diseased gallbladder with the additional possibility of neuroma formation as suggested by Womack and Crider.[46] Intravenous cholecystography, using the newer drugs, may be of value in such instances, and if the cystic duct stump is not filled with stones, it may be visualized.

A plain roentgenogram of the gallbladder

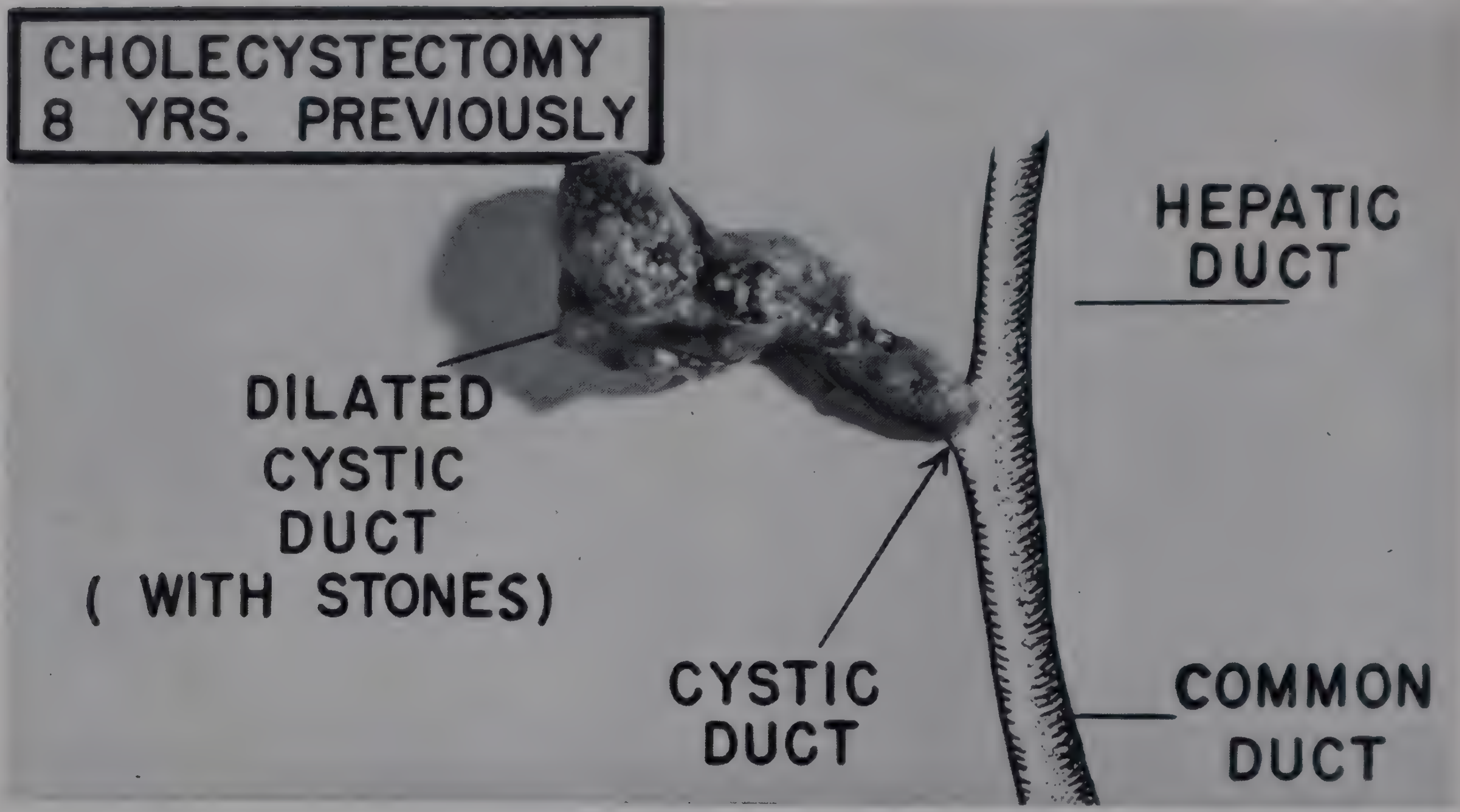


FIG. 243. A remnant of the cystic duct overlooked at the time of cholecystectomy is a common cause of postcholecystectomy symptoms. At the time of operation a remnant of cystic duct measuring an inch or longer is found frequently, and nearly 3 out of 4 of the retained ducts contain small stones or gravel.

region may demonstrate calculi beneath the twelfth rib. Even in the absence of positive x-ray findings patients with severe and classical symptoms warrant exploration. At the time of operation a remnant of cystic duct measuring 1 inch or longer is frequently found, and nearly 3 out of 4 of the retained ducts contain small stones or gravel (Fig. 243). The increasing number of reports in the current literature suggests that a cystic duct remnant may be a frequent source of postcholecystectomy symptoms. The fear of serious consequences of injury to the common duct probably explains the attitude of some surgeons toward its incomplete removal. However, the careful dissection and demonstration of the junction of the cystic and the common ducts permits complete removal of the cystic duct, with little chance of injury.

CALCULUS OF COMMON DUCT

There is another group of patients in whom the symptomatology arises from an overlooked common duct stone. Unless the common duct is opened in nearly 50 per cent of the cases and common duct stones recovered in 20 per cent or more of these, the best results cannot be expected.

Fortunately, the number of accidents at the time of biliary surgery resulting in stricture formation is not too great, but all surgical clinics are confronted with a few of these patients every year. It is well to reemphasize that there are more anomalies of the blood supply and ducts in the region of the gallbladder than in almost any other part of the body, and great care must be exercised in technic in even the simplest of cases.

DUODENUM ADHERENT TO GALLBLADDER FOSSA

In many instances of re-exploration the duodenum is found to be firmly adherent to the gallbladder fossa. A previously performed gastro-intestinal series usually has failed to demonstrate any duodenal obstruction, but distortion is in evidence. Even though the surgeon should restore the anatomy to as near normal as possible by release of the adherent duodenum, it is difficult to believe that this condition would cause severe symptoms since it is a common occurrence following cholecystectomy. Until such time as this problem is settled, one should not only carefully reperitonealize the gallbladder fossa after cholecystectomy but also place the omentum between the liver and duodenum in order to prevent its formation.

Once the physician has exhausted all forms of medication, if after thorough investigation of the patient, including a flat plate for stones and a complete gastrointestinal, cardiac and renal survey, he is convinced that the patient has a lesion which is causing symptoms similar to those preceding removal of the gallbladder, exploration is advisable. In a large proportion of such thoroughly screened patients, the difficulty can be corrected.

RESIDUAL DISEASE OF BILIARY TRACT

There is a fourth group of patients in whom residual disease of the biliary tract including cholangitis, hepatitis or "biliary dyskinesia," apparently occurs. It is unwise to accept such a diagnosis without the thorough study described. Early surgery with complete removal of all biliary pathology may decrease the number of such patients, but there is no specific treatment, either medical or surgical, routinely efficient in alleviating symptoms once present.

INJURY TO THE EXTRAHEPATIC DUCTS

REPAIR AT TIME OF INJURY

In rare instances the common duct may be divided or ligated accidentally during operation for gallstones. This unfortunate injury is most likely to occur just below the junction of the hepatic and the cystic ducts for reasons already presented. The surgeon must recognize the error at the time of operation and take steps to restore the continuity of the bile duct immediately so as to avoid prolonged disability, multiple operations or an operative fatality.

Under such circumstances a direct end-to-end anastomosis is preferred. Every effort must be made to be certain that there will be no tension on the suture line. To this end, the peritoneum to the right lateral side of the duodenum is divided and is mobilized upward and to the patient's left duodenum. Mattress sutures of silk are taken in the hepatoduodenal and gastrohepatic ligaments anchoring the duodenum upward. Clamps are not applied to the severed ends of the ducts. Should the edges be uneven or frayed, they are trimmed evenly to permit accurate approximation of the duct as in blood vessel suturing with both ends of the duct held in position by means of guy sutures of fine silk. A single layer of interrupted inverting mattress sutures of No. 0000 silk are placed posteriorly, taking care not to enter the lumen of the duct, inasmuch as the presence of nonabsorbable suture might invite stone formation. These sutures should not be placed too far from the edge, because stenosis or stricture may occur if too much duct wall is turned in at the suture line.

Upon completion of the posterior layer the common duct is exposed for a sufficient distance, preferably downward, to permit the introduction of a small open-end catheter. This catheter is passed up to and beyond the suture line so as to ensure an adequate lumen for the duct after completion of the anterior portion of the anastomosis and to maintain decompression during the postoperative recovery period. The catheter must not be placed at the suture line for fear of an inflammation and subsequent fibrosis and scarring of the anastomosis.

If the duct has been divided quite low, a small T-tube is inserted into a second opening in the hepatic duct; the lower limb of the tube is passed inferiorly and to a position distal to the line of repair. Using a small French needle and No. 0000 silk throughout, each suture must be placed accurately and should include only a minute bite of tissue if stenosis is to be avoided.

After the anastomosis has been completed, saline is injected into the catheter to make certain that there is no leakage about the suture line. A final inspection is made to be certain that there is no tension on the suture line, and if suspected, additional anchoring sutures are taken in adjacent tissues.

Several Penrose drains are placed in the subhepatic area, taking care that they do not lie next to the anastomosis; then the opposite ends of the rubber drains and the common duct catheter are brought out through a

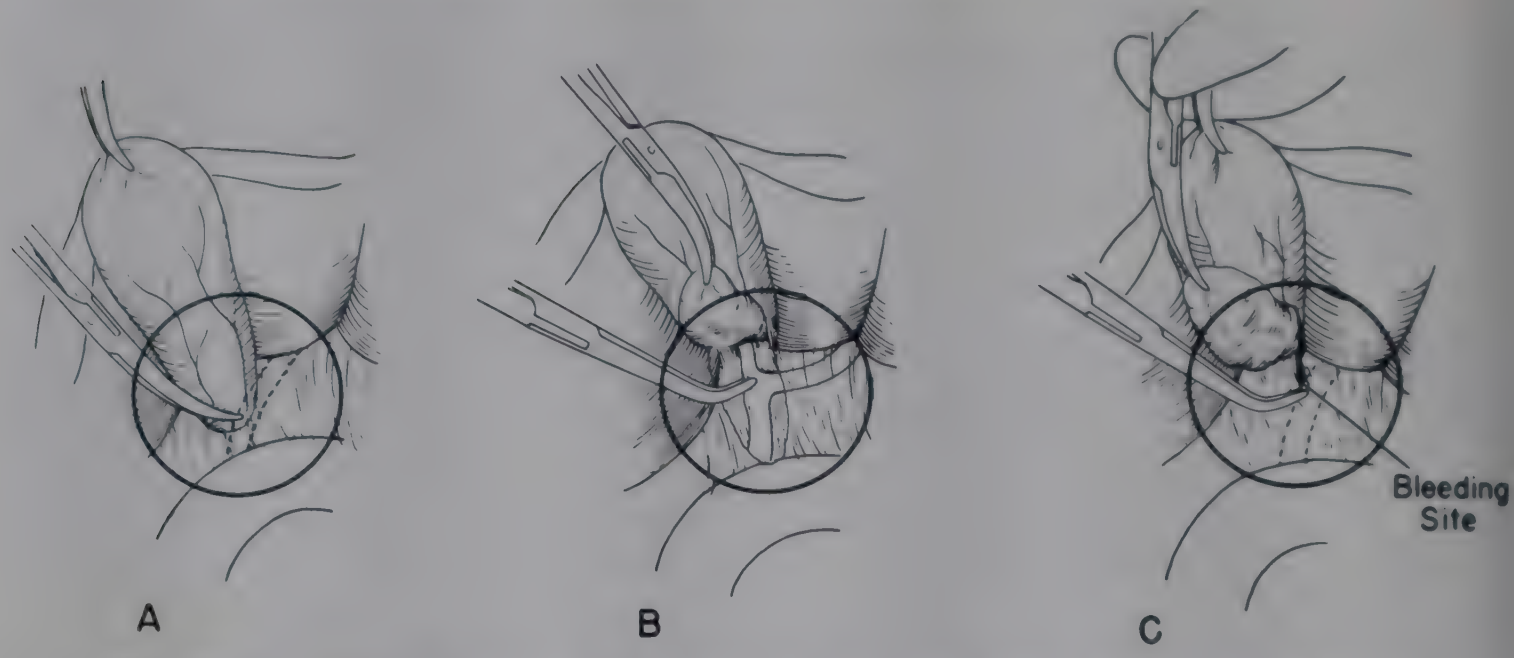


FIG. 244. Accidental injury to the common duct may result from: (A) Failure to mobilize the ampulla, (B) angulation of the common duct, (C) blind application of clamp to bleeding point.

stab wound to the right of the incision. The drainage tube is anchored securely to the abdominal wall with a silk suture. The omentum is turned upward into the subhepatic space, and the wound is approximated, using interrupted No. 2-0 silk on the peritoneum and the fascia.

If jaundice is anticipated or the patient's general condition is poor, wound closure is reinforced best with heavy silk stay sutures. Inasmuch as the rubber in the common duct drainage tube incites considerable reaction, it is best to remove it within two weeks, but not until one is satisfied with biliary perfusion pressures and the anastomosis demonstrated by a postoperative cholangiogram.

STRICTURES

Strictures of the extrahepatic bile ducts may result from erosion of a calculus or prolonged inflammation, but the majority are due to technical difficulties or surgical errors at the time of operation.

Etiology. Three situations commonly lead to stricture formation (Fig. 244):

1. The surgeon, unable to control bleeding at the time of cholecystectomy, may blindly clamp and ligate part or all of an extrahepatic bile duct.

2. The surgeon may fail to recognize the ampulla lying parallel with and adjacent to the common duct so that clamps applied before the ampulla has been divided sufficiently may lead to crush injury or even complete division of that portion of the common duct.

3. Traction on the cystic duct or the gallbladder angulates a mobile common duct so sharply that unless the structures about the cystic duct are clearly defined, the common duct may be included in the cystic duct ligature.

Prevention. The surgeon can prevent these technical mistakes by following carefully each detail of the operative procedure and by resorting to cholecystostomy or removal of the gallbladder from the fundus downward when the anatomy in the region of the cystic and common ducts is distorted by extensive inflammation.

Technics for Repair. Strictures of the common hepatic and common bile ducts are among the most difficult problems that confront the surgeon. Inasmuch as several types of stricture are encountered, a number of methods have been developed for their repair. The most satisfactory method of handling an injury of the bile duct in a particular patient cannot be determined until the involved area has been thoroughly exposed. Therefore, the surgeon must be acquainted with the several technics.

HEINEKE-MIKULICZ PLASTIC. Constriction as a result of temporary application of a clamp to the ducts (crush injury) leads to short strictures and is best managed by the principle of Heineke-Mikulicz. Traction sutures are placed on either side of the isolated duct, and an opening is made either above or below the stricture, depending upon the space available. A small probe or grooved director is inserted past the constriction, and with the metal director in place an incision is made through the constricted area. An open-end catheter is passed through the previously made opening in the duct below the point of stricture, is directed beyond the constricted area and is anchored in position with an interrupted silk suture.

The duodenum is mobilized by the Kocher technic so that there will be absolutely no tension on the suture line at the completion of the plastic closure of the duct. In general, the distance gained by mobilization must be greater than the length of the vertical incision in the common duct. If the duodenum has been drawn up toward the hilus of the liver as a result of previous cholecystectomy, mobilization is unnecessary. The mobilized duodenum is pulled upward and to the left and anchored to the hepatoduodenal and the gastrohepatic ligaments with interrupted silk sutures. Then the opening in the duct at the point of stricture is approximated in the opposite direction with interrupted fine silk sutures. The traction sutures are manipulated gently until the upper and the lower lips of the opening are approximated. Interrupted silk sutures are taken to include only the margin of the cut duct. The closure is reinforced with a second layer of interrupted silk sutures. The security of the suture line is tested by injecting saline through the catheter, and a final inspection is made to ensure the absence of tension. The area is covered with omentum, a Penrose drain is inserted into the operative area, and the abdomen is closed in routine fashion.

Choledochoduodenostomy. The anastomosis of the stump of the proximal duct directly to the duodenum is the simplest procedure when both ends of the duct are not available for a direct repair. If the stump of the proximal duct cannot be found, one should not hesitate to continue the dissection high up into the hilus of the liver. Aspiration for bile with a fine hypodermic needle may be of value in identifying the upper portion of the duct. The dissection is continued until a sufficient segment of duct is isolated to permit direct anastomosis to the duodenum.

This method is preferred to the previous practice of instituting tube drainage and depending upon the formation of an external fistula. Once the fistula did form, it required implantation, and it was rare indeed that one stayed open.

After the dissection has been carried well up toward the hilus of the liver, and the dilated stump of duct is isolated, traction sutures of fine silk are taken in opposite sides of the duct. The field is walled off with Mikulicz pads, and with a small, sharp knife an incision is made directly into the bulbous structure. Constant suction is maintained to prevent soiling of the operative area. The initial incision should be small, for it can be lengthened later or the anterior lip can be divided at right angles to the original incision as desired.

The duodenum is anchored securely with mattress sutures up to a point where the anastomosis can be carried out without any tension on the suture line. With the lumen of the duct held open by traction sutures of fine silk, the duct is anchored with interrupted silk sutures to the anterior duodenal wall at its superior margin, taking care that the sutures do not enter the lumen of the duodenum or the duct. A small incision is made into the duodenum parallel to the serosal sutures. If a 2-layered anastomosis is preferred, then the mucous membrane is approximated, using interrupted No. 4-0 silk sutures with the knot always on the inside. The anterior reinforcing row of interrupted silk sutures should be placed close to the initial suture line to avoid turning in more tissue than necessary. The procedure is facilitated by completing the anastomosis over a rubber tube which may prevent undue stenosis of the suture line.

A small rubber tube about 5 mm. in diameter, depending upon the size of the ducts, and about 6 to 8 cm. long is inserted for a short distance upward into the common duct and down into the duodenum after the initial posterior layer of anastomosis is completed. This is anchored to the duct with a fine silk suture which is tied very tightly so that it will slough through in a few days. The anterior wall is closed easily with a single layer of interrupted silk sutures. If, upon inspection, there is tension on the suture line, the duodenum is freed further and re-anchored with mattress sutures on each side of the site of anastomosis.

Direct anastomosis of the two ends of the duct with preservation of the sphincter of Oddi is probably the most satisfactory method of restoring biliary continuity,[11] although it seldom is feasible except at the time of injury. On occasion, however, as suggested by Cattell and Lahey, the uninjured portion of the common duct may be isolated by splitting the head of the pancreas following its mobilization.[33] When dealing with a short stump of common hepatic duct, the use of a Y-tube inserted into the two limbs of the hepatic duct is helpful.

Choledochoduodenostomy and choledochojejunostomy are the two procedures used most frequently for late repair of a severed biliary tree. In the latter instance, the proximal duct may be anastomosed to a loop of jejunum with a proximal entero-enterostomy or to a Roux-en-Y arm of jejunum. Proximal decompression is made possible by means of a rubber catheter inserted into the proximal jejunum and threaded past the anastomosis. Then the opposite end is brought to the outside through a stab wound as in a standard jejunostomy.

A variety of procedures other than those described have been recommended, and the surgeon operating upon the patient with stricture should be familiar with all in order to select the one best suited for overcoming the technical difficulties encountered.

TUMORS OF THE GALLBLADDER

Benign Tumors

Types. Benign tumors of the gallbladder occur in some 4 per cent of those removed at operation. Papillomas and adenomas are encountered most frequently, but fibromas, lipomas and cystadenomas have been reported. The typical papilloma with its many hyperplastic villi filled with cholesterol crystals resembles the "strawberry" type gallbladder and is thought to be the end result of a metabolic or infectious disease. The polypoid or sessile type papilloma is not ordinarily associated with malignancy but on rare occasions may be the precursor of a local carcinomatous outgrowth. Adenomas of the gallbladder are less common and for the most part occur in the fundus. These lesions seem to project above the mucosa on the cholecystogram and are easily palpable in the gallbladder at operation.

Diagnosis of benign tumors is difficult because they produce few complaints. Cholecystography provides the only method of diagnosing benign tumors before operation; however, they are usually an incidental finding at surgery for associated gallstones. In retrospect, it is difficult to distinguish symptoms referable to gallstones from those originating from a benign tumor. In rare instances a polypoid adenoma may intermittently obstruct the cystic duct and produce biliary colic.

Treatment. Cholecystectomy, performed for the relief of gallbladder disease, is adequate treatment for benign tumors found at operation. If a nonmalignant tumor in a noncalculous gallbladder is suspected on repeated x-ray examinations, cholecystectomy should be considered to establish the correct diagnosis and to rid the patient of a possibly premalignant lesion.

Carcinoma

Incidence. Another and more serious lesion to be considered as a potential complication of gallstones is carcinoma of the gallbladder. At autopsy, from 5 to 10 per cent[40] of all malignancies encountered reportedly arise in the gallbladder—an overall incidence of 0.27 to 0.41 per cent in the general population. Carcinoma of the gallbladder occurs in some 2.5 per cent of all patients operated upon for cholecystic disease. The incidence of malignancy increases to 9 per cent in patients over 60 requiring a cholecystectomy. Gallbladder malignancy occurs most commonly in patients 50 to 70 years of age; however, it has been reported in patients as young as 23 years of age.

Gallstones with Malignancy. Gallstones are found in 70 to 80 per cent of all patients with a gallbladder carcinoma which in itself is 4 times more frequent in females than in males. This fact, together with the increased frequency of gallstones in women, further suggests that prolonged mucosal irritation from gallstones might predispose to malignant change. Perhaps this would influence the physician to consider early cholecystectomy for gallstones, not only as a means of correcting associated symptoms or preventing later complications of acute cholecystitis and common duct stone but also as a prophylactic measure against malignant transformation. At least fewer patients would enter cancer age still having an abnormal gallbladder.

Diagnosis. Carcinoma of the gallbladder is notoriously an insidious disease and is rarely seen sufficiently early to permit resection for cure. The diagnosis is seldom made prior to operation unless the mass is large and the patient has a concomitant history suggestive of malignant disease, including weight loss, cachexia and the like. Although carcinoma of the gallbladder occurs most frequently in the older age group, an occasional malignancy is found in younger patients having a cholecystectomy for gallstones and suggests early cholecystectomy whenever gallstones are proved.

Symptoms. Inasmuch as most of these patients have gallstones, the presenting symptoms are similar to those of chronic cholecystitis and cholelithiasis. Right-upper-quadrant pain, which may be a continuous dull ache or intermittent and cramplike, simulating true biliary colic, is a frequent complaint. Unlike chronic cholecystitis and cholelithiasis, however, the symptoms of carcinoma are progressive with no tendency toward remission. Jaundice is common and results from large metastatic glands in the porta hepatis or direct extension to the extrahepatic bile ducts. Therefore, clinical and laboratory findings in obstructive jaundice indicate far-advanced malignancy. An abdominal mass and weight loss are present in nearly half of the cases. Gradual obstruction of the cystic duct results in a tense globular distention not unlike a benign hydrops. If the fundus is involved, a hard mass may be palpable in the right upper quadrant.

Surgical Treatment. Even when the diagnosis of gallbladder carcinoma has been made, only about half of the cases warrant exploration. Three out of every four patients subjected to surgery are found to be inoperable and in the majority biopsy only should be attempted. It should be pointed out that the life expectancy has not been altered, regardless of operation, and the 5-year survival rate following surgery varies from zero to 6 per cent.

A cholecystectomy and wedge resection of the adjacent liver parenchyma is the procedure of choice. Cholecystectomy alone for carcinoma should be considered a palliative operation because, although the tumor seems to be limited to the gallbladder wall, it has already extended into the liver or to a more distant site in most cases. If metastases and extension have occurred already, an exploration and biopsy of the lesion serves to establish the diagnosis and the prognosis of the disease. Despite widespread metastases, palliation may be accomplished. Biliary decompression for relief of jaundice or pruritus is certainly worthwhile. A gastro-enterostomy may control or prevent nausea and vomiting secondary to obstruction due to malignant invasion.

Contraindications to Surgery. Fixation of the tumor mass to the anterior abdominal wall, a large nodular liver indicative of metastases, or malignant ascites should be considered as definite contraindications to surgery. Such lesions may show temporary response to radiation, but in general no form of treatment is too rewarding because metastasis has already occurred by the time the diagnosis is made.

TUMORS OF THE EXTRAHEPATIC BILE DUCTS

Incidence. Primary carcinoma of the extrahepatic bile ducts, exclusive of the ampulla of Vater, is not too uncommon. A recent series of 100 consecutive jaundiced patients was found to have tumors of the bile duct in some 10 per cent.

Types. Pathologically there are two types —the nodular and the papillary—and of these the first is most frequent, comprising 90 per cent of the total. Papillomatous growths in the bile ducts obstruct the lumen before penetrating the wall and produce symptoms before metastasis.

Symptoms. Carcinoma of the bile ducts occurs in patients somewhat older than those with carcinoma of the gallbladder or of the head of the pancreas and leads to early total jaundice. The onset is acute, and loss of weight and strength is not uncommon. Chills and fever from secondary ascending cholangitis are frequently present. There may or may not be a past history of biliary tract disease.

Diagnosis of carcinoma of the bile ducts cannot be made previous to operation. If the lesion occurs below the junction of the cystic and the hepatic ducts, the gallbladder may be enlarged and so may be used for a short-circuiting operation to relieve the patients of symptoms due to intense jaundice.

Surgical Treatment. Resection is feasible in only rare instances and when attempted calls for considerable ingenuity in restoring ductal continuity. Implantation of the proximal end of the duct into the duodenum is most satisfactory and at times the ampulla and the cystic duct of the normal gallbladder may be substituted for the common hepatic and the common bile ducts.

CARCINOMA OF HEAD OF PANCREAS

Incidence. Carcinoma of the head of the pancreas occurs more often than carcinoma of the gallbladder or the bile ducts, and along with common duct stones it accounts for most cases of obstructive jaundice. The physician usually can differentiate from the history and the physical findings between jaundice-producing neoplasm and common duct stone with some degree of accuracy.

Diagnosis. Involvement of the gallbladder and the extrahepatic bile ducts with carcinoma offers little opportunity of early diagnosis and, in turn, relatively few malignancies producing obstructive jaundice can be removed surgically. Exploration, however, may be worthwhile, since relief of the icterus and its disagreeable symptoms is possible in a high percentage of patients. Therefore, the physician should recommend surgical exploration whenever the diagnosis of obstructive jaundice due to tumor is made. This is true whether the obstruction is primary in the biliary tract or the head of the pancreas or secondary to extrinsic pressure from metastatic glands. On occasion a small neoplasm arising from the ampulla of Vater or the head of the pancreas is found and resected successfully. Furthermore, regardless of how hopeless the situation may appear and how definite the diagnosis of malignancy may be, the surgeon may find a calculus instead of neoplasm as the source of disease.

Surgical Treatment. Adequate attention to the details of preoperative preparation as outlined under the treatment of jaundice is necessary to ensure a low morbidity and mortality rate in these poor-risk patients. Neither age nor etiology is a contraindication to surgery in extrahepatic jaundice, since the cause can be removed or palliation provided in a large number of cases.

OPERATION FOR MALIGNANT OBSTRUCTION

The abdomen is opened through a right paramedian incision which is placed slightly lower than is customary in cholecystectomy. Every bleeding point is ligated to avoid, if possible, the danger of postoperative hemorrhage. The abdomen is explored thoroughly for evidence of metastasis, and the local cause of the distended gallbladder is determined. The area of the common hepatic and the hepatic ducts likewise is inspected to rule out involvement by carcinoma or extrinsic pressure from metastatic glands as is so frequently the case in carcinoma of the head of the pancreas.

Every effort must be made to be certain that the obstruction is malignant and not secondary to an impacted calculus. Differentiation of a benign lesion, such as chronic pancreatitis, from carcinoma of the common duct or the head of the pancreas may try the ingenuity and the skill of the most experienced surgeon. Biopsy of the head of the pancreas is rarely of help, since frozen section diagnosis is usually chronic pancreatitis even when neoplasm is present. The use of the Silverman needle as suggested by Kirtland[31] is of advantage for deep-seated tumors.

The problem is particularly difficult if one finds no evidence of a mass on palpation. This often means that a very small tumor is involving the lower end of the common duct in the region of the ampulla of Vater; however, a calculus or even a benign polyp in the ampulla may be at fault. Under these circumstances, choledochostomy, operative cholangiography or transduodenal exploration of the ampullary region may be required. If the patient is elderly or a poor operative risk, and if the gallbladder and the bile ducts are thin-walled with no evidence of calculus, it is better to decompress the biliary tree rather than attempt a more nearly accurate diagnosis, by choledochostomy or duodenostomy. Decompression is accomplished by anastomosing the gallbladder to the stomach, the duodenum or the jejunum.

Although some surgeons prefer to use the stomach for palliative anastomosis because of its proximity to the enlarged gallbladder, the small intestine is equally accessible, and the thickness of its wall more nearly approximates that of the gallbladder. Furthermore, the jejunum is less likely to become involved with malignancy by extension than either the stomach or the duodenum.[7] The proximal jejunum is held up to the gallbladder to determine the feasibility of anastomosis without tension, taking into account the fact that once the obstruction is relieved, the liver and the attached gallbladder will recede to their normal positions in the right upper quadrant. The application of straight enterostomy clamps will permit a more nearly accurate anastomosis; in addition, they control bleeding and minimize contamination. The field is thoroughly walled off with gauze sponges. That portion of the jejunum which lends easy approximation to the gallbladder is used in the anastomosis.

Once the site is selected and before the gallbladder is aspirated, a layer of interrupted sutures is taken to include the serosa of the gallbladder and the jejunum for a distance of 3 to 4 cm., the angle sutures being left long for traction. Since the gallbladder wall is often very thick, great care must be exercised in placing these sutures so that the wall is not torn. Then a large needle is inserted into the fundus of the gallbladder, and its contents are aspirated by suction, making every effort to avoid bile contamination within the peritoneal cavity. An incision is made both in the jejunum and in the gallbladder to permit a stoma as large as feasible. Then the mucosa is approximated with closely placed interrupted silk sutures so as to avert postoperative hemorrhage. The standard Connell-type stitch is used to close the anterior part of the anastomosis.

Following the completion of the mucosal suture, a second anterior layer of interrupted sutures is placed between the gallbladder and the jejunum. It is always advisable to reinforce the angles.

It may be advisable to carry out a side-to-side entero-enterostomy if subsequent resection is not contemplated.[35] More recently, a side-to-side pancreatojejunostomy or anastomosis of the jejunum to the duct of Wirsung has been suggested as a means of assuring improved nutrition and minimizing the likelihood of pancreatitis from obstruction of the pancreatic duct.[6] Ligation of the gastroduodenal and the inferior pancreatoduodenal arteries may be worthwhile in controlling growth of the primary tumor.

If the lesion is small and there is no evidence of lymph node metastasis or infiltration of the portal or the superior mesenteric veins, then radical resection is indicated. A one-stage pancreatoduodenostomy is advisable unless the general condition of the patient contraindicates extensive operation. If such is the case, operation for relief of the obstructive jaundice should be planned so as to permit resection of the head of the pancreas at some later date.

The one-stage procedure does not reduce the magnitude of the second operation, inasmuch as the sole objective of cholecystojejunostomy is relief of the obstructive jaundice. The jejunal loop is brought anterior to the colon, and the anastomosis is placed at least 15 to 18 inches from the ligament of Treitz, and entero-enterostomy is deferred so as not to add to the mechanical difficulties of the second stage. In either case, an upper right paramedian incision is employed.

Having ruled out local and distant metastasis, the peritoneum to the lateral side of the duodenum is incised, and the duodenum and the head of the pancreas are mobilized to the left. The lesser sac is entered by freeing the gastrocolic omentum of its attachment to the hepatic flexure and the transverse colon, and the inferior pancreatoduodenal artery is divided and ligated. The gastrohepatic omentum is incised, and the right gastric and the gastroduodenal arteries are divided between clamps and ligated. The common bile duct is dissected free of the portal vein and divided below the cystic duct. Then the neck of the pancreas may be separated from the portal vein and the superior mesenteric vessels by finger dissection. The stomach is divided between clamps 3 inches proximal to the pylorus, a Pott's clamp is placed across the pancreas, and the latter organ is divided at the junction of the body and the neck. The cut surface is approximated with interrupted mattress sutures, leaving the pancreatic duct free for subsequent anastomosis. The ligament of Treitz is incised, the proximal jejunum is mobilized and divided, and its proximal portion passed beneath the superior mesenteric vessels. The uncinate process, the third and the fourth parts of the duodenum and the remainder of the head of the pancreas are freed by dividing the small vessels arising from the superior mesenteric vessels.

A variety of methods have been reported for re-establishing continuity of the biliary, the pancreatic and the upper gastro-intestinal tracts.[8, 44] The modifications commonly used have been designed to minimize regurgitation of gastric or intestinal contents into the biliary and the pancreatic tracts so that ascending infection may be avoided. At the present time there is no general agreement as to the preferred technic.

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